

The Chemistry of Open-Chain Organic Nitrogen Compounds

volume I

*Functions Derived from Ammonia: Amines, Amides,
Imines, Nitriles, Isocyanates, etc.*

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The Chemistry of Open-Chain Organic Nitrogen Compounds: Volume I

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For One Who Is Dearest
and Others Who Are Also Very Dear

Preface

The organic chemistry of nitrogen has been an active exciting field at frequently recurring periods since Wöhler's synthesis of urea from ammonium cyanate and A. W. Hofmann's classic investigations of amines. Though both are now more than a century old, interest and excitement has not diminished. Nevertheless, few books have been devoted solely to this subject. One of the few, however, stands out clearly from the others: the delightfully written work by Neville Vincent Sidgwick, first published approximately forty years ago, in which countless chemists have found valuable help. It is now, unfortunately, long out of date, and its author is no longer with us, but all who write on the subject now and for some time to come are in his debt.

The purpose of my book is to give an interpretive as well as descriptive survey of the chemical behavior of functional groups containing nitrogen. The enormous field of heterocyclic compounds is excluded, in part because of its size and in part because it is adequately treated elsewhere. Polyfunctional and multifunctional compounds, such as amino acids, nitro alcohols, etc., have been largely ignored in order to keep the subject to manageable size. I have compiled the material for this book selectively rather than encyclopedically; although specific compounds and examples of a given reaction are severely limited, I have tried to be more comprehensive with respect to the kinds of reaction that each functional group has been observed to undergo.

The emphasis of this book is on reactions, with a moderate amount of information on mechanism when it seems that it might be helpful, whereas synthesis is assigned a secondary role. This is not really as arbitrary as it may seem, for most preparative methods for one type of organic nitrogen compound involve the reactions of another. In cases where this is not so, I have given a more extended treatment to the preparative reaction than otherwise. The references given in the sections on preparative methods have been primarily chosen to lead the reader to sources that are outspokenly devoted to synthesis, such as *Organic Syntheses*, *Organic Reactions*, and Houben-Weyl, as well as to appropriate journal articles.

I have chosen the references from a frugal utilitarian viewpoint, restricting them largely to those I thought would be most useful, in order to avoid suffocating the reader (and myself) in the vast morass of literature in the field. Reviews, summarizing articles, and leading references have been given preference over those representing earliest reports, and readily accessible sources have been strongly favored. All of this has meant that the publications (but I hope not the chemistry) written in languages other than English, German, and French appear infrequently among the references, and that the discoverer or major developer of a reaction may not necessarily have his articles referred to directly. No slight is intended, and I have tried to make sure that the omitted references could be found easily in the sources actually cited. Another consequence is that the bibliography is heavily biased in favor of recent publications.

The writing was completed in the summer of 1964. Some references up to the last moment are included, but some contributions that should have been included have undoubtedly been overlooked, especially in the most recent period, and probably from earlier periods as well. If this book is helpful, however, it will have served its intended task.

It is a pleasure to acknowledge the hospitality of Professor H. Brederick and the Institut für Organische Chemie in Stuttgart, which gave me the opportunity to begin the writing and bring it substantially forward during a sabbatical leave granted by the University of Michigan. The tolerant understanding of my family has allowed it to be completed; I thank them for so cheerfully putting up with both its primary and secondary domestic effects.

The willingness of my colleagues, students, and other friends in the chemical world to answer questions, engage in discussions, and to read and criticize portions of the manuscript from a lone paragraph to whole chapters has given me not only material aid, but much-appreciated moral encouragement. I thank them all most gratefully. Finally, the painstaking criticism of Professor Nathan Kornblum on virtually all details, from the major to the very minor, has allowed me to bring this book to a state of accuracy and clarity that I could not have achieved alone; it is a pleasure to record my thanks and appreciation for his wonderful help.

PETER A. S. SMITH

Ann Arbor, Michigan
June 1965

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*chapter
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Survey of Inorganic Nitrogen Compounds

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Since much of the material in this book is presented in relation to the respective inorganic nitrogen compounds whose substitution products comprise organic nitrogen chemistry, it is worthwhile to put these inor-

ganic parent substances on record.¹ Their properties are often useful for reference in interpreting the behavior of their organic derivatives. The number of distinct inorganic compounds of nitrogen with hydrogen and oxygen, excluding salts, is surprisingly large, but there are still some structures that are known only as organic derivatives; these are included here for the sake of completeness.

Starting at the lowest state of oxidation, ammonia, we have certainly the most important parent compound for organic nitrogen chemistry.² It liquefies at atmospheric pressure only when cooled to -33° , but can be obtained in the liquid state at ordinary temperatures under moderate pressure, contained by stout, sealed glass test tubes. Even so, the boiling point is much higher than can be accounted for solely in terms of molecular weight; methane, for example, has almost the same molecular weight, but boils at -161.5° , and one has to go to propane, with almost three times the molecular weight of ammonia, to find a hydrocarbon of comparable boiling point. It is clear, therefore, that there are considerable intermolecular forces in ammonia; these are largely hydrogen-bonding forces.

Liquid ammonia is a colorless, mobile liquid; since it freezes at -78° , its liquid range is much shorter than that of water. The density of liquid ammonia, 0.7 g/ml at the boiling point, is also less than that of water, as is the heat of vaporization (327 cal/g—cf. ΔH_{vap} for water, 539 cal/g). Since both of these properties as well as the boiling point are closely related to intermolecular forces, it is clear that intermolecular forces are weaker in ammonia than in water; this illustrates the generalization that hydrogen bonds between nitrogen atoms are weaker than those between oxygen atoms.

The heat capacity of liquid ammonia is unusually high (1.05–1.1 cal/g), and is one of the few that exceed water. The dielectric constant, 22.7 at -50° , is high compared to most organic liquids, but is much lower than that of water (*ca.* 80 at ordinary temperatures); it falls as the temperature rises. The self-ionization of ammonia is quite small, but detectable, $(\text{NH}_4^+)(\text{NH}_2^-) = 10^{-33}$ at -33° , but is markedly lower than that of ethanol ($K = 10^{-19}$) and of water ($K = 10^{-14}$). The observable self-ionization of ammonia is mostly a consequence of its pronounced basicity ($K_b = 1.8 \times 10^{-5}$), for it is an extremely weak acid, having a strength only about as great as diphenylmethane.

As a solvent, liquid ammonia has a remarkably wide action; both inorganic salts in wide variety and most organic compounds (except most saturated hydrocarbons) generally dissolve significantly. Since the amide ion, NH_2^- , is a very strong base, liquid ammonia is a good solvent in which to obtain a strongly basic medium.

An unusual and very important property of liquid ammonia is its

ability to dissolve the alkali and alkaline earth metals reversibly. The solutions are colored very dark blue, the color being independent of the metal. The solutions have exceptionally strong reducing power as well as electrical conductivity, and it is believed that an anionic species describable as a solvated electron is responsible for these properties.

Ammonia stands out among other inorganic nitrogen compounds as being remarkably stable; its heat of formation from the elements is 11 kcal/mole (cf. the commercial Haber process for ammonia synthesis). It will nevertheless burn readily to form nitrogen and water.

The geometry of the ammonia molecule ³ is of considerable interest from a theoretical standpoint. It has been determined that the molecule is pyramidal, with the nitrogen at the apex about 0.4 Å above a triangular base defined by the three hydrogen atoms; the H—N—H angle is unfortunately not precisely known, the best value being $106.6 \pm 4^\circ$. The fact that the molecule is far from planar eliminates the possibility of sp^2 hybridization for the N—H bonds; a completely unhybridized structure, in which the N—H bonds are formed by the three p -orbitals of nitrogen, would demand 90° angles between the hydrogens. The actual angle is assumed to result from mutual repulsions among the hydrogens; sp^3 hybridization would be required to provide sufficient orbital overlap at this angle. Alternatively, Fajans ^{3c} prefers to consider the ammonia structure as resulting from three protons imbedded in the highly polarizable electron cloud of N^{-3} , the four atomic cores taking positions determined by the balance between their mutual repulsion and their attraction for electrons.

Expansion of the coordination sphere of the nitrogen atom, as in the formation of the ammonium ion, brings about a change to a completely tetrahedral structure, just as in methane, with full sp^3 hybridization.

The energy barrier for the inversion of the ammonia pyramid, that is, the process in which the molecule passes through a fully planar structure and then forms a new pyramid with the apex on the other side, is well below the average energy of thermal collisions at ordinary temperatures. ^{3b,d} This means that the molecules are ordinarily in a state of relatively rapidly oscillating inversion.

Although ammonia shows pronounced quantitative differences in its properties compared to water, there is still an over-all qualitative similarity, about which very much has been written. The quantitative ratios between the base strengths, or the acid strengths, of ammonia and water remain roughly the same with similar substitution, so that, for example, a knowledge of the ratio (a factor of *ca.* 10^{11}) for the inorganic parent substances can be used to make a rough estimate of the acid strength of an amide from the more easily measured value of the corresponding acid.

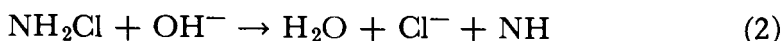
NH (AZENE, IMIDOGEN, IMENE, OR NITRENE)

The species NH has been variously called "imine radical" or "imide radical" in the older literature. The term "nitrene" has been used widely in recent literature; it was, however, long ago pre-empted for an entirely different structural grouping. The term "azene," also of early vintage, will be used here; a variant, "azylene," to make the term parallel with "methylene," has also been suggested, and the term "imene" has found favor in the German literature. "Imidogen" is used by *Chemical Abstracts*.

Azene is a highly reactive substance that was detected spectroscopically long before it (or a polymer) was isolated as a blue solid stable only at liquid-air temperatures. Its chemistry has been but little investigated. Disproportionation into nitrogen and ammonia or into ammonium azide, attack on C—H and N—H bonds with the introduction of amino groups, and hydrogen abstraction to form an amino radical, seem to be the usual chemical behavior.⁴ Azene has been suggested as an intermediate in the Haber ammonia synthesis, which under certain conditions can be made to produce traces of hydrazine (by the reaction $\text{NH} + \text{NH}_3 \rightarrow \text{NH}_2\text{—NH}_2$?), and in the formation of aniline from the reaction of ammonia with oxygen in the presence of benzene. It is presumably the initial product of the decomposition of hydrogen azide (Eq. 1), and may

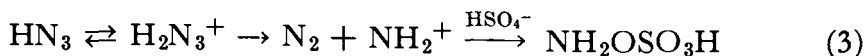


also result from the action of strong bases on chloramine (Eq. 2). The



organic derivatives are on the whole no more stable, but appear to be important intermediates in a number of reactions. It seems likely that in the ground state, azene and its derivatives are in a triplet state, with two unpaired electrons, but they may often be produced in an excited, singlet state by the energetic reactions that generate them.

The conjugate acid of azene, NH_2^+ , is isoelectronic with the simplest carbonium ion, CH_3^+ . Although there is no direct evidence of its existence, it seems not unlikely that it would be present if NH were generated in the presence of acids; the acid-catalyzed decomposition of hydrogen azide quite possibly involves this species, as, for example, in the formation of hydroxylamine-O-sulfonic acid from hydrogen azide and fuming sulfuric acid⁵ (Eq. 3). Reactions of organic hydroxylamines and azides



can be readily correlated by such a supposition.

AMINO RADICAL, $\text{NH}_2^\bullet$

This species has not yet been isolated except ⁴ in a frozen krypton matrix at 4.2 Å, but there is convincing evidence that it is formed in solution and perhaps in the gas phase by thermal decomposition of hydrazine. When generated in solution ⁶ by the reduction of hydroxylamine with vanadous or titanous salts, it shows behavior similar to a hydroxyl radical; it adds to carbon-carbon double bonds, and initiates polymerization. Organic derivatives of the amino radical probably occur as reactive intermediates in some oxidation-reduction reactions, and are formed reversibly in the thermal cleavage of tetraaryl hydrazines.⁷

The formation of the conjugate acid of the amino radical, $\text{NH}_2^\bullet + \text{H}^+ \rightarrow \text{NH}_3^+$, is in principle possible. Such ion-radicals may be formed in solution when the reactions presumed to generate $\text{NH}_2^\bullet$ are carried out in the presence of acids. Organic derivatives are known in the form of salts stable enough to permit isolation.

HYDROXYLAMINE

Hydroxylamine,^{2b} which is the parent of oximes, hydroxamic acids, amine oxides, and many heterocyclic systems, is very familiar in the form of its salts; the free base, however, is not nearly so commonly seen. It is a crystalline solid, mp 33°, stable enough to be isolated, but not enough to permit storage. It is extremely soluble in water, hygroscopic, and sensitive to air. Heating brings about decomposition before the atmospheric boiling point is reached; extrapolation of boiling points at reduced pressures gives an approximate boiling point at 760 mm of 125°. Comparison to the properties of ammonia shows the marked effect of the stronger hydrogen-bonding power of the hydroxyl group.

Hydroxylamine is a somewhat weaker base ($\text{pK}_b = 8.04$ at 25°)⁸ than ammonia, and only a little stronger than aniline and pyridine. Its acidic properties are appreciable, apparently similar to those of water, but the instability of hydroxylamine in strongly basic solutions has prevented measurement.

The structure of hydroxylamine under ordinary conditions is justifiably taken to be that implied by the name, $\text{HO}-\text{NH}_2$. However, it is in principle capable of tautomerism to ammonia oxide, $^-\text{O}-\text{NH}_3^+$. Such a tautomer has not been detected, but it may quite well be present in a small equilibrium concentration in solution; the conjugate acid, NH_3OH^+ , is identical from both tautomers, of course. The presence of charge separation in the ammonia oxide structure is reason to expect it to be of higher energy than the hydroxylamine structure; this expectation is sup-

ported by the comparison between organic amine oxides and hydroxylamines. X-ray crystal structure determinations for hydroxylamine hydrochloride and hydrobromide give a value of 1.45 Å for the N—O distance.⁹

The supposition that hydroxylamine can accept a proton on the oxygen atom as well as the nitrogen serves to explain certain acid-catalyzed reactions. The structure $\text{H}_2\text{N—OH}_2^+$ would, of course, be expected to be much less stable than $\text{H}_3\text{N}^+\text{—OH}$, since reduced nitrogen is much more strongly basic than oxygen; nevertheless, a sufficient amount of the less stable tautomer could be present in acidic solutions to permit it to be a reaction intermediate. In very strongly acidic solutions, two protons might be accepted, giving the structure $\text{H}_3\text{N}^+\text{—OH}_2^+$. Because of the adjacent like charges, such a structure would be of high energy, but it is not entirely unreasonable in view of the ready formation of the isoelectronic hydrazine cation, $\text{H}_3\text{N}^+\text{—NH}_3^+$.

Hydroxylamine is readily reduced and readily oxidized. Reduction gives ammonia as an end product, but under some circumstances, at least, the reaction $\text{NH}_2\text{OH} + (\text{e}^-) \rightarrow \text{NH}_2 + \text{OH}^-$ is the initial step. Oxidation gives various products, depending on the agent and the conditions. Ferric ion is mild enough to allow the removal of only two hydrogens; the result is nitroxyl, HNO , whose properties will be discussed shortly, and which is rapidly converted to nitrous oxide. Most other oxidizing agents give higher oxides of nitrogen.

Hydroxylamine is thermodynamically unstable with respect to nitrogen, hydrogen, and water, but it more easily decomposes into ammonia, water, nitrogen, and nitrous oxide.

HYDROXYLAMINO RADICAL

The oxidation state represented by the tautomers $\text{H}_2\text{N—}\ddot{\text{O}}\cdot$ and $\cdot\ddot{\text{N}}\text{—OH}$ is known in inorganic chemistry only in the form of more complex compounds, such as $(\text{KO}_3\text{S})_2\text{NO}$ (Fremy's salt), which can be isolated as a stable, yellow solid.¹⁰ This salt is apparently largely a dimer in the solid state, but dissociates reversibly to a monomer in solution. Organic derivatives of the type Ar_2NO are known.

NITROXYL, HNO

Nitroxyl has been isolated (from photolysis of methyl nitrite) only when frozen in a solid argon matrix, but there is abundant spectroscopic evidence for it in the gas phase and chemical evidence for it in solution.¹¹ The formation by the careful oxidation of hydroxylamine with ferric ion

has been mentioned; it can apparently also be formed by reductive processes, and by the combination of nitric oxide with atomic hydrogen (Eq. 4). Its sodium salt is stable enough for isolation and storage at



room temperature; it is formed by direct combination of sodium dissolved in liquid ammonia with nitric oxide. Spectroscopic evidence favors the structure $\text{H}-\text{NO}$, with an $\text{H}-\text{N}-\text{O}$ angle of approximately 110° .¹²

Nitroxyl can apparently be both reduced and oxidized, but its usually overwhelming tendency is to dimerize, producing hyponitrous acid, $\text{H}_2\text{N}_2\text{O}_2$; this is itself not very stable, and soon dehydrates to nitrous oxide. The appearance of nitrous oxide in many reactions, inorganic and organic, appears to be best explained by the intermediate formation of nitroxyl. The ready dimerization is also shown by the organic derivatives of nitroxyl, the nitroso compounds.

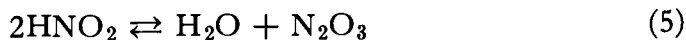
NITRIC OXIDE AND ITS HYDRATE, HYDRONITROUS ACID

Since organic nitrogen compounds are customarily considered as products of substitution of a hydrogen by an organic group, there can be no organic derivatives of nitric oxide. Hydronitrous acid, H_2NO_2 , corresponds to the same oxidation state, however, and is in principle the parent compound for organic derivatives. The acid has never been isolated; however, its sodium salt, Na_2NO_2 , can be isolated as an explosive solid from the reaction of sodium in liquid ammonia on sodium nitrite.^{2a}

The hypothetical acid can be written in two tautomeric forms: $\cdot\ddot{\text{N}}(\text{OH})_2$ and $\text{HO}-\text{NH}-\ddot{\text{O}}\cdot$. Organic derivatives of either form are unknown, but perhaps only for want of sufficient trying; anion radicals detected during the reduction of nitro compounds are presumably derived from the latter form.

NITROUS ACID

Nitrous acid is known only in solution or in the form of salts, for it rapidly equilibrates with its anhydride (Eq. 5), which further equilibrates



with nitric oxide and nitrogen dioxide (Eq. 6). Because of this, the struc-

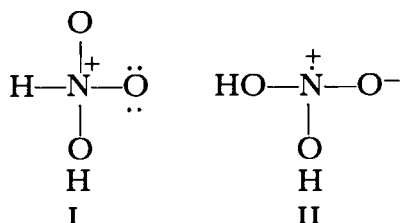


ture of nitrous acid cannot be determined precisely, although there seems to be little doubt that it is largely if not entirely in the form $\text{HO}-\text{N}=\text{O}$.

It is an acid of moderate strength, K_a being 4.6×10^{-4} . It also displays feeble basicity in strongly acid solutions, giving rise first to the nitrous acidium ion, H_2NO_2^+ , and then the nitrosonium ion, NO^+ .

NITROGEN DIOXIDE AND ITS HYDRATE, H_2NO_3

Nitrogen dioxide is familiar as the red-brown gas that equilibrates readily with its colorless dimer, N_2O_4 . Neither compound can give rise to organic derivatives by replacement of hydrogen, of course, but the hypothetical hydrate, H_2NO_3 , can. It has been proposed as an intermediate in the reduction of nitric acid. One can imagine two structures



for such a compound (I, II); however, stable organic derivatives are not known of either structure.

NITRIC ACID

Little needs to be said about nitric acid, whose structure, $\text{HO}-\text{NO}_2$, allows only esters as organic derivatives. It is a strong acid, but only a little stronger than H_3O^+ , and also has feeble basic properties. These show up in strongly acid solutions, and give rise to the nitric acidium ion, H_2NO_3^+ , and nitronium ion, NO_2^+ . Nitric acid is thermodynamically unstable at high concentrations, and spontaneously liberates oxygen.

HYDRAZYL RADICAL, N_2H_3 , AND ITS CONJUGATE ACID

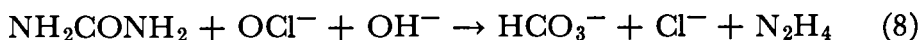
The first stage in the oxidation of hydrazine, N_2H_3 , has not been isolated, nor have the salts of its conjugate acid, N_2H_4^+ ; however, there is evidence that it is an intermediate in the oxidation of hydrazine, and perhaps in the reduction of hydrogen azide.^{7, 13} Organic derivatives of the hydrazyl radical and of its conjugate acid have been isolated. It has been suggested that hydrazyl exists in quantity on Jupiter and may contribute to the colors displayed by the planet; firsthand verification is eagerly awaited.

HYDRAZINE

Hydrazine,¹⁴ $\text{H}_2\text{N}-\text{NH}_2$, is a colorless liquid with a liquid range quite close to that of water; its boiling point is 113.5° , and its freezing point 2° . It forms an extremely stable hydrate, bp $119-120^\circ$, from which it is released only by solid alkali. Although it is thermodynamically unstable with respect to nitrogen and ammonia, or nitrogen and hydrogen, it can be stored readily when free of catalytic impurities. In the presence of suitable metallic catalysts, it is a convenient source of hydrogen for reductions *in situ*. It is markedly basic, being only a little weaker than ammonia, and stronger than hydroxylamine; pK_b is 5.93. It is capable of picking up a second proton, giving the ion $\text{H}_3\text{N}^+-\text{NH}_3^+$, an interesting species because of its adjacent positive charges, whose structure has been verified by X-ray crystal structure determination.¹⁵ As would be expected, the basicity of N_2H_5^+ is very low, apparently close to that of H_2O ; however, diacidic salts such as $\text{N}_2\text{H}_4 \cdot 2\text{HCl}$ can be crystallized readily from water solution. Hydrazine can be prepared by several practical methods, such as the reaction of ammonia with chloramine (Eq. 7) or hydroxylamine-O-sulfonic acid, and the hypochlorite oxidation



of urea (Eq. 8), as well as by several reactions of less importance.



Hydrazine is isoelectronic with hydroxylamine and hydrogen peroxide, with which useful comparisons can be made. Like them, it can be both oxidized and reduced, but it is least active as an oxidizing agent. Reduction can only cleave the N—N bond, but oxidation can proceed through several formal intermediates before N_2 is reached. Something of the chemistry of these intermediates is given elsewhere in this chapter.

The N—N distance in hydrazine, $1.47 \text{ \AA}$, falls to 1.42° in the dication.¹⁵

 $\text{NH}_2-\text{NH}-\text{NH}_2$ AND HIGHER HOMOLOGUES

No saturated hydronitrogens larger than hydrazine have been positively identified in the unsubstituted state, although a solid that appeared to be tetrazane has been isolated¹⁶ at -195° ; it decomposes at -178° exothermically to N_2 and NH_3 . Substitution derivatives of a four-nitrogen chain are well characterized, however.

DIAZENE OR DIIMIDE, $\text{HN}=\text{NH}$ OR $\text{H}_2\text{N}^+=\text{N}^-$

Although organic derivatives of both structures of N_2H_2 are well known, the parent compound has only recently been isolated as a yellow solid, stable at liquid-air temperatures.¹⁷ There is, however, reasonably good evidence that $\text{HN}=\text{NH}$ can be obtained in solution,¹⁸ whereupon it rapidly decomposes by alternate paths into ammonia and nitrogen, ammonium azide, or hydrazine and nitrogen. Oxidation of hydrazine and catalytic dehydrogenation have been extensively investigated as routes to diazene. The decarboxylation of azodicarboxylic acid, $\text{HOOC}-\text{N}=\text{N}-\text{COOH}$, is also a source. Diazene appears to be a powerful hydrogen donor, and as such has received attention recently as a reducing agent in organic chemistry. This property would, obviously, be expected to disappear with substitution. Diazene is apparently much less readily reduced than oxidized. The structure $\text{H}_2\text{N}^+=\text{N}^-$ is represented in organic chemistry by diazo compounds, $\text{R}_2\text{C}=\text{N}_2$, and compounds of the type $\text{R}_2\text{N}^+=\text{N}^-$ (azamines).

POLYAZENES

It is in principle possible to have unsaturation in longer chains of nitrogen atoms, as in triazene, $\text{HN}=\text{N}-\text{NH}_2$. Although no unsubstituted compounds of this type have yet been isolated, there is evidence that triazene is formed in the oxidation of hydrazine, but breaks down rapidly to nitrogen and ammonia. A blue solid with the composition $(\text{NH})_x$, isolable at liquid-air temperatures, has also been suggested¹⁹ to be triazene; it is transformed at -125° into NH_4N_3 . Organic derivatives of triazene and tetrazene-1 and -2 are well known. The properties of the organic derivatives lead one to expect the inorganic parents to have both weakly acidic and weakly basic properties, and to be very unstable with respect to loss of nitrogen.

AZADIENES AND AZAPOLYENES

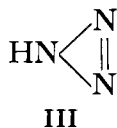
Unsubstituted compounds of this type, such as $\text{HN}=\text{N}-\text{N}=\text{NH}$, have never been isolated. There is good reason to believe that they would be extremely unstable toward loss of nitrogen. Organic derivatives of pentazadiene, $\text{HN}=\text{N}-\text{NH}-\text{N}=\text{NH}$, and hexazadiene, $\text{HN}=\text{N}-\text{NH}-\text{NH}-\text{N}=\text{NH}$, are known, however; they are inclined to be unstable and explosive. An organic derivative of an azatriene, octazatriene, has also been reported.

HYDROGEN AZIDE (HYDRAZOIC ACID)

The existence of a substance with the formula HN_3 astonished and delighted the first investigators, and continues to surprise students when they are told of it for the first time; proofreaders even yet occasionally "correct" the formula to " NH_3 ." Hydrogen azide^{2b} is a weak acid of almost the same strength as acetic acid; $K_a = 2 \times 10^{-5}$. This property has given rise to the alternative name "hydrazoic acid"; in the older literature, "azoimide" is often encountered. Hydrogen azide also shows feeble basic properties in the presence of concentrated mineral acids; pK_b has been estimated as -6.2 , which is several orders of magnitude weaker than water. It has also been suggested that a second proton can be accepted in extremely acidic media, giving the species $\text{H}_3\text{N}_3^{++}$.

Hydrogen azide is a colorless liquid of boiling point 37° , just above that of ethyl ether. It is a highly energy-rich compound, being thermodynamically unstable with respect to nitrogen and hydrogen to the extent of 319 kcal/mole. Although it can be isolated in the pure state, it is extremely sensitive, even at low temperatures, and is violently explosive. Its sensitivity seems to be increased by aging for a short time, as suggested by the fact that it has often been distilled, only to explode in an hour or less while standing undisturbed. It is completely miscible with water and organic solvents, however, and in solution, even as concentrated as 10%, can be handled without fear, as long as precautions are taken to prevent evaporative fractionation (the presence of some substance of the same boiling point, such as pentane or ether, is a good safeguard). Although the heavy metal salts are usually sensitive and explosive, the commercially available sodium salt is relatively innocuous; it has been routinely ground in a mortar and can even be decomposed smoothly by controlled heating into nitrogen and metallic sodium. The aluminum salt, which has useful properties in organic synthesis, is usually prepared *in situ* by reaction of aluminum chloride with sodium azide.

The structure of hydrogen azide was at first thought to be cyclic, that is, triazirene (III).



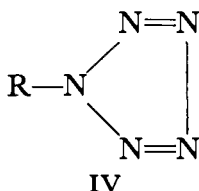
It has since been shown by physical means that the nitrogen chain is linear, with the hydrogen held at an angle. The ion in crystalline salts is symmetrical. These facts have been additionally supported by demonstration with the nitrogen-15 isotope that in the ion two of the nitrogen atoms are equivalent, but not all three.

The representation of these facts by a valence formula has been accomplished in more than one way. Franklin ²⁰ and later Fajans ^{3c} have preferred to consider the azide ion as a completely ammonolyzed nitrate ion, and write the molecule as $\text{HN}=\text{N}^{\text{5}+}\text{N}^{\text{3}-}$. Resonance between the two Lewis structures $\text{HN}::\overset{+}{\text{N}}::\text{N}::\text{N}^{\text{3}-}$ and $^-\text{HN}::\overset{+}{\text{N}}::\text{N}::\text{N}$ is commonly considered to represent the molecule; in the ion, these two structures become exactly equivalent. In molecular orbital terms, there is delocalization of *pi*-electrons over all three nitrogen atoms.

A five-nitrogen relative of hydrogen azide, formulable as $\text{HN}=\text{N}-\overset{+}{\text{N}}=\text{N}=\text{N}^-$, etc., apparently exists as organic derivatives, the diazoazides, which thus far have proved too unstable to isolate.

CYCLIC HYDRONITROGENS

The cyclic structure originally attributed to hydrogen azide has apparently not yet been encountered; all organic azides studied have been found to have the linear structure. However, substituted pentazoles (IV)



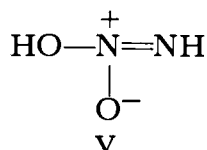
have been isolated in crystalline form.²¹

NITROSAMIDE

Nitrosamide, $\text{O}=\text{N}-\text{NH}_2$, is tautomeric with two other forms, $^-\text{O}-\overset{+}{\text{N}}\text{H}=\text{NH}$ and $\text{HO}-\text{N}=\text{NH}$. No compound corresponding to any of these structures has been isolated, in spite of many attempts. The reaction of nitrous acid with ammonia (the decomposition of ammonium nitrite) gives molecular nitrogen and water as the only detectable products, but it seems certain for mechanistic reasons that one of the forms of nitrosamide must be an intermediate. Some monosubstituted and many disubstituted organic derivatives of the first form, the nitrosamines, are known, and derivatives of the second form are known as azoxy compounds. A few monosubstituted compounds that might correspond to any of the three forms are known (Chapters 11 and 15); their acidic character suggests that nitrosamide would also be weakly acidic, as, indeed, would be predicted from the known acid strength of nitrous acid and the general relation between the properties of corresponding $-\text{NH}_2$ and $-\text{OH}$ compounds.

NITRAMIDE

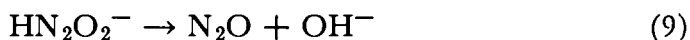
The amide of nitric acid, $\text{O}_2\text{N}-\text{NH}_2$, can be isolated as a crystalline solid, mp $72-75^\circ$; it presumably equilibrates readily with the tautomeric *aci*-form (V);



organic derivatives of both forms are known.²² As can be predicted from the acid strength of nitric acid, nitramide is markedly acidic ($K_a = 2.6 \times 10^{-7}$). It is unstable, and cannot be stored; decomposition gives nitrous oxide and water. Although it is presumably an intermediate in the decomposition of ammonium nitrate, it has not been isolated from that reaction; it is best prepared by hydrolysis and decarboxylation of nitrourea.

HYPONITROUS ACID AND NITROSOHYDROXYLAMINE

Hyponitrous acid is an explosive, colorless, crystalline solid that cannot be stored as such, but solutions acidified to pH 0 to 3 can be kept for several days if a free-radical-trapping inhibitor is present.²³ The mono-anion decomposes rapidly into nitrous oxide and hydroxide (Eq. 9); a

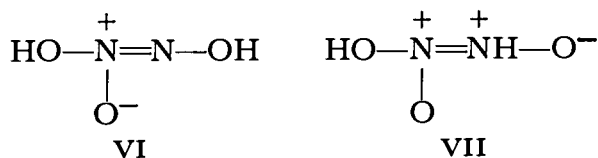


free-radical chain reaction leading to nitrogen and nitric acid is a significant decomposition path for the free acid. Hyponitrous acid is dibasic ($K_1 = 9 \times 10^{-8}$; $K_2 = 10^{-11}$). Its structure is probably $\text{HO}-\text{N}=\text{N}-\text{OH}$, in a *trans* configuration. However, since no other compound of the same molecular formula is known, we cannot be sure that we are not dealing with one of the tautomeric structures, $\text{O}=\text{N}-\text{NHOH}$ or $^-\text{O}-\text{NH}^+=\text{NH}^+-\text{O}^-$, or an equilibrium mixture of them. A purely inorganic derivative of nitrosohydroxylamine is known in the form of salts of the formula $\text{M}_2[\text{O}_3\text{SN}_2\text{O}_2]$.²⁴ Organic derivatives are known of all three structures, those of the last being the dimers of C-nitroso compounds.

NITROHYDROXYLAMINE (NITROHYDROXAMIC ACID)

Nitrohydroxylamine, $\text{O}_2\text{N}-\text{NHOH}$, is easily obtained as its sodium salt, which is stable in the solid state but decomposes rapidly in solution.¹¹ The free acid has not yet been isolated, but the properties of the salt in aqueous solution indicate that both hydrogens are more acidic than water,

although hydrolysis of the divalent anion is apparently appreciable. The free acid may obviously exist in two other tautomeric forms (VI, VII).



NITROSOHYDRAZINES AND TRIAZENE OXIDES

The reaction of nitrous acid with hydrazine produces hydrogen azide; nitrosohydrazine, $\text{ON}-\text{NH}-\text{NH}_2$, is presumably an intermediate, but it dehydrates too rapidly to allow isolation. Organic derivatives of both nitrosohydrazine and N,N' -dinitrosohydrazine are known, however. There are three other tautomeric structures: $\text{HN}=\text{N}-\text{NHOH}$, $\text{HN}=\overset{+}{\text{N}}-\text{NH}_2-\text{O}^-$, and $\text{H}_2\text{N}-\text{N}=\text{N}-\text{OH}$. Organic derivatives of at least two of them have been isolated, but the unsubstituted compounds remain unknown.

NITROHYDRAZINE

No substance corresponding to the structure $\text{O}_2\text{N}-\text{NH}-\text{NH}_2$ or its *aci*-form, $\text{H}_2\text{N}-\text{N}=\text{NOOH}$, has yet been isolated.

HYDROXYTRIAZENE

Although the unsubstituted compound, $\text{HO}-\text{NH}-\text{NH}-\text{NH}_2$, has not been detected, organic derivatives have been reported.

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chapter
two

Aliphatic Amines

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NOMENCLATURE

Although aliphatic amines are classified as primary (RNH_2), secondary (R_2NH), tertiary (R_3N), and quaternary ($\text{R}_4\text{N}^+\text{OH}^-$), these terms are never used in the naming of individual compounds. The alkyl groups are named in the ordinary way, and followed by the suffix “-amine” —for example, “methylamine,” “diethylamine.” When two or more different groups are present, it is customary to follow one or another systematic order of precedence; *Chemical Abstracts* uses alphabetical order, but size is also used. The names of the separate alkyl groups are strung together as one word, it being assumed from the absence of locant prefixes that each group is attached to nitrogen; thus: “ethylpentylamine,” $\text{C}_2\text{H}_5\text{NH}(\text{CH}_2)_4\text{CH}_3$, and “2-ethylpentylamine,” $\text{CH}_3\text{CH}_2\text{CH}_2-\text{CH}(\text{C}_2\text{H}_5)\text{CH}_2\text{NH}_2$. When there may otherwise be ambiguity, parentheses or the locant “N-” may be used; thus “(chloromethyl)amine,” $\text{Cl}-\text{CH}_2-\text{NH}_2$, and “N-chloro-N-methylamine,” $\text{Cl}-\text{NH}-\text{CH}_3$ (“methylchloramine” is unambiguous for the latter compound, but the order of the substituents is contrary to precedence rules). Only in complicated

compounds, particularly where some other structure may take precedence in determining the root name, is the prefix "amino-" used, as in "2-aminocyclohexanone."

Salts are best named by using the same rules applied to the root "ammonium," although salts of the hydrogen halides are usually named by following the name of the amine with "hydrochloride," etc. The prefix form for the group —NH_3^+ is "ammonio."

PROPERTIES

The substitution of an alkyl group on ammonia brings about important quantitative changes, but leaves the molecule qualitatively very similar. Methylamine boils at -6° , just 27° higher than ammonia, and the methyl group has thus added the usual increment to the boiling point resulting from molecular weight increase. Methylamine is a markedly stronger base than ammonia, its ionization constant, 4.4×10^{-4} , being about 20 times greater. The other straight-chain primary amines have similar properties, as shown in Tables 2-1 and 2-2. Branching adjacent to the amino group has the usual effect of lowering the boiling point compared to the straight-chain isomer, as shown by *tert*-butylamine, bp 45° , and also may cause a small reduction in the base strength of primary amines (K_b for *tert*-butylamine is 2.8×10^{-4}). The straight-chain primary amines are all liquids (or gases) at room temperature until dodecylamine is reached.

Further substitution of ammonia does not produce a simple increase in boiling point; although dimethylamine boils 13° above methylamine, trimethylamine boils only 9.5° above it (see Table 2-1). With heavier alkyl groups, there is a continuous rise from primary to tertiary amine, but it is not quite as steep as would be expected from considerations of molecular weight alone. These phenomena are adequately explained when changes in hydrogen bonding are taken into account. Substitution

Table 2-1 *Boiling points of aliphatic amines*

R	R—NH ₂	R ₂ NH	R ₃ N
CH ₃	-6°	7°	3.5°
C ₂ H ₅	16.5°	55.5°	89.4°
<i>n</i> -C ₃ H ₇	50°	110.7°	156°
<i>n</i> -C ₄ H ₉	77.8°	161°	214°
<i>iso</i> -C ₄ H ₉	69°	140°	191.5°
<i>sec</i> -C ₄ H ₉	66°	132°	
<i>tert</i> -C ₄ H ₉	45°	95°	

Table 2-2 *Base strengths of aliphatic amines*
(mostly based on data collected by Hall ⁹)

R	($-\log K_b$ for $B + H_3O^+ \rightleftharpoons BH^+ + H_2O$)		
	R—NH ₂	R ₂ NH	R ₃ N
CH ₃	3.38	3.36	4.24
C ₂ H ₅	3.37	3.02	3.35
<i>n</i> -C ₃ H ₇	3.47	3.00	3.35
<i>iso</i> -C ₃ H ₇	3.37	2.95	
<i>n</i> -C ₄ H ₉	3.41	2.75	3.11
<i>iso</i> -C ₄ H ₉	3.58	3.50	3.68
<i>sec</i> -C ₄ H ₉	3.44	2.99	
<i>tert</i> -C ₄ H ₉	3.55		
<i>tert</i> -C ₄ H ₉ - <i>tert</i> -C ₅ H ₁₁ -CH ₃			2.1 *

* C. Ainsworth and N. R. Easton, *J. Org. Chem.*, **26**, 3776 (1961).

of the second hydrogen of ammonia by even a methyl group apparently reduces hydrogen bonding significantly, and the substitution of all three hydrogens stops it. Even so, the boiling points of tertiary amines are usually slightly higher than the saturated hydrocarbon of the same molecular weight and degree of branching (compare isobutane, bp -10° , with trimethylamine, bp 3.5°); this effect can be attributed to the appreciable dipole moment of tertiary amines.

The effect of substitution on the base strength of alkylamines is more complicated and has been the object of much discussion. The general trend is for a second alkyl group to increase the strength only a small amount over the primary amine, and for the third to decrease the base strength compared to the secondary amine, and sometimes to a value lower than that of the primary amine (see Table 2-2). The simple alkylamines are all stronger than ammonia, however.

Although the increased basic strength of primary amines over ammonia can be attributed to the electron-donating effect of alkyl groups, it is obvious that such an effect is insufficient to explain the relationship of the basicities of secondary and tertiary amines. This problem has been the object of much interest, and has evoked two types of explanation, one based on steric crowding, the other on solvation (in which steric effects may also play a role). H. C. Brown and coworkers ¹ have championed the proposition that the base-strengthening inductive effect of alkyl groups is opposed by increasing steric crowding. The concept is based on the assumption that in trimethylamine (and other trialkylamines), the alkyl groups are spread apart by mutual repulsion to something greater than the tetrahedral angle, so that the tertiary amine has the form of a pyramid more flattened than those of less substituted amines. Conversion to the

ion by addition of a proton imposes a nearly tetrahedral structure on the species, thus bringing the alkyl groups closer together and subjecting them to steric compression.

This type of effect, called "B-strain," thus does not operate against the incoming proton, but between the groups already present on the nitrogen. Support for this proposition has been adduced from measurements of the base strength of amines against acids bulkier than the proton, such as metal ions and trialkylboranes. When the acid species or the groups on the nitrogen are sufficiently large, the apparent basicity of amines drops steadily with increasing substitution, indicating essentially complete domination by steric effects. This, however, must be largely a case of repulsion between the alkyl groups and the large incoming acid, so-called "F-strain," and is thus really a separate type of phenomenon.

When the B-strain theory of the origin of base-strength anomalies was propounded, there was insufficient evidence about the structures of amines to enable a judgment to be made on such a basis. There have been, however, estimates of the magnitude of the energy effects expected to result from the degree of steric crowding that would be involved, and these were held to be too small to account for the observed basicity effects.² More recently, a value of $108^{\circ}40' \pm 1^{\circ}$ has been obtained by micro-wave spectroscopy for the C—N—C angle in trimethylamine.³ Even at its upper limit, this value is scarcely larger than the tetrahedral angle ($109^{\circ}28'$); to the extent that this value is accurate, the argument for increased steric crowding in the cation as the cause of the depressed base strength of tertiary amines is vitiated, for the methyl groups would actually be farther apart in the tetrahedral ion.

The proposition that solvation is of major importance in determining the differences in base strength among different types of amines has been advanced by various authors. It is based on the observed large heat of hydration of ammonium ion (85 kcal/mole) compared to ammonia and amines (10–12 kcal/mole), and estimates that the heat of hydration of the uncharged amine should not vary greatly in magnitude with alkylation, while that of the ammonium ion should decrease by about 8 kcal/mole for each replacement of H— by CH₃—. ⁴ The decrease in hydration energy with increasing substitution by itself should lead to a continuous decrease in basic strength with alkylation; the balance between such an effect and the base-strengthening inductive effect of alkyl groups could reasonably lead to the observed order: secondary > primary > tertiary > ammonia.⁵ The cause of the decreasing hydration energy with substitution can be understood by assuming either that the degree of hydrogen bonding depends on the number of available hydrogens on the nitrogen,⁶ or that the accumulation of alkyl groups on nitrogen interferes with the interaction of the ionic charge with water molecules.⁷ In

support of these views are observations of a pronounced role of the solvent on the order of relative basicity.^{4, 8} In chloroform, chlorobenzene, or ethylene chloride, for example, where solvation energies would be expected to be small, the basic strengths increase continuously with alkylation, and trimethylamine is the strongest of the methylated amines. However, in heptane, benzene, or dioxane, the secondary amine is the strongest,⁴ whereas in ethyl acetate, the primary is strongest. It is clear that the solvent exerts a considerable influence on relative basicities, and the role of solvation must be large. (For the influence of steric effects of a different kind on base strengths, cf. the discussion of aromatic amines, p. 88.)

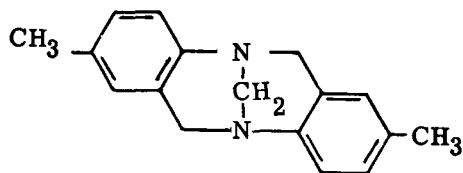
H. K. Hall⁹ has correlated the base strengths of an impressive number and variety of amines on the basis of the concept of solvation in combination with R. W. Taft's modification of the Hammett equation, in the form $\text{pK}_a = -\rho^* \Sigma \sigma^* + c$, where σ^* is a substituent constant expressing the polar effect of each substituent on the nitrogen, ρ^* is a reaction constant expressing the sensitivity of base strengths to polar effects, pK_a is $-\log K_a$ for the respective ammonium ions, and c is a constant corresponding to pK_a° (for primary amines, $\rho^* = 3.14$, $c = 13.23$; for secondary, $\rho^* = 3.23$, $c = 12.13$; for tertiary, $\rho^* = 3.30$, $c = 9.61$). Small deviations in the form of base strengths slightly lower than predicted are observed in cases where steric interference would be expected, but such effects appear only with primary and secondary amines and are absent in tertiary amines even in apparently favorable cases, such as *t*-amyl-*t*-butylmethylamine, pK_b 2.1.

The importance of the electric effects of polar substituents, even though transmitted through saturated carbon atoms, is shown by ethanolamine, pK_b 4.5, much weaker than ethylamine, and by morpholine, $\text{O}(\text{CH}_2\text{-CH}_2)_2\text{NH}$, pK_b 5.64, much weaker than piperidine, $\text{CH}_2(\text{CH}_2\text{CH}_2)_2\text{NH}$, pK_b 2.78. The highly hindered amines, 1,2,3,6,6-pentamethylpiperidine, pK_b 2.75, and *t*-amyl-*t*-butylmethylamine, are the strongest tertiary amines yet encountered, presumably owing to the polar effect of the methyl groups (cf. *N*-methylpiperidine, pK_b 3.92).

The absence of apparent steric effects with tertiary amines, and their presence with primary, appear to be in conflict with the theory that B-strain is the major factor determining the order of basicity, but can be encompassed by the solvation approach if one considers that solvation of the lone N—H bond of tertiary ammonium ions can involve only one solvent-molecule (e.g., water) attached frontally, but solvation of secondary and primary ammonium ions, with more sites for solvation, may involve clusters of solvent molecules, so as to intensify steric crowding. Regardless of the explanation, Hall's proposal has been shown to have effective quantitative predictive value.

Quaternary ammonium hydroxides, $R_4N^+OH^-$, are completely ionized and have the base strength of hydroxide ion. Because the nitrogen atom is tetravalent and therefore cannot expand its coordination sphere, and there are no hydrogens active in hydrogen bonding, association of the ions cannot go beyond the stage of loose clusters. Even in the solid state, quaternary ammonium hydroxides resemble alkali metal hydroxides; they are colorless, hygroscopic, caustic substances, very difficult to obtain dry. They cannot, of course, be distilled, and decompose on heating (Hofmann degradation, see p. 53).

The tetrahedral arrangement of substituents in quaternary amines has been demonstrated not only by crystal-structure determinations, but also by the resolution into optically active forms of compounds having four different alkyl groups, such as allylbenzylmethylanilinium salts. Resolution of tertiary amines of the type $RR'R''N$ is in principle possible, since the pyramidal structure is then unsymmetrical, but success cannot be anticipated with ordinary amines under ordinary conditions, because spontaneous racemization is extremely rapid (cf. the rapid inversion of ammonia, Chapter 1), even though the frequency of inversion¹⁰ might be slowed down by increasing bulk of the substituent groups, or by more rigid structural arrangements such as are encountered in cyclic compounds. "Tröger's base" is a tertiary amine in which such inversion is not possible; it has been successfully resolved by chromatography on an optically active adsorbent, d-lactose hydrate.^{10c}



Amines are both good solutes and good solvents. The simple alkylamines are slightly more soluble in water than the corresponding alcohols, and the threshold size for water solubility by customary qualitative organic analysis criteria is six carbons. Amine salts are nearly all quite soluble in water when the size is moderate, but among amines of more than ten carbons, it is not uncommon to find hydrochlorides that dissolve in benzene and can be precipitated from alcoholic solution by adding water. Amine salts can generally be relied on to be insoluble in petroleum ether, however.

Liquid amines have solvent properties similar to ammonia and dissolve many inorganic substances as well as most organic compounds. The alkali carbonates and hydroxides are quite insoluble, however, and the latter are preferred drying agents for amines. This selective solvent property has given rise to the commercial use of amines to leach out traces of alkali chlorides from alkali hydroxides. The alkali metals are

soluble in dry liquid amines only in traces (except for lithium, which is more soluble), in contrast to their large solubility in liquid ammonia, but apparently this small solubility is enough to confer special reducing properties on metal-amine mixtures. The combination, especially in the presence of small amounts of alcohol, has found wide use as a delicate reducing agent in organic chemistry ("Birch reductions").¹¹

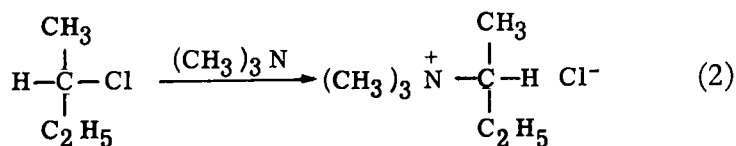
REACTIONS

SALTS Salt formation is probably the simplest reaction of amines, and certainly the commonest. Because of its ease and the enormous effect it has on the solubility, it has become indispensable in the preparation and purification of amines. A salt that is good for enabling an amine to be extracted into water for separation from nonbasic substances may not be at all suitable for ultimate isolation and purification of the amine, however. Thus, amine hydrochlorides are often conveniently soluble in water, but too often they are hygroscopic, difficult to crystallize, or high melting. It is for this reason that picrate salts of amines—which are usually only slightly soluble, readily crystallized, and of conveniently measured melting point—are so often prepared. Styphnates (salts of trinitroresorcinol) and picrolonates (salts of 1-*p*-nitrophenyl-3-methyl-4-nitro-5-pyrazolone) are also used for the same reasons.

ALKYLATION The unshared electron pair of amines (primary, secondary, and tertiary) gives them nucleophilic as well as basic properties—that is, they are anionoid displacing agents. The simplest manifestation of this property is in alkylation¹² with alkyl halides, etc., such as the reaction of trimethylamine with methyl iodide (Eq. 1). Such reactions



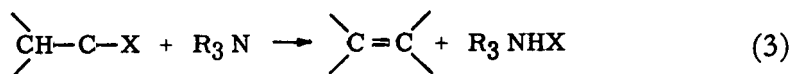
have been found to follow second-order kinetics: rate = k (amine) (RX). The reactions may occur so readily as to be spontaneous without a solvent, but they are fastest in polar solvents, such as alcohols, etc., and negligibly slow in dilute solution in petroleum ether. Such a solvent dependence is a natural consequence of the generation of charge separation in the transition state. In the alkylation of amines, inversion of configuration can be expected when the carbon atom that forms the new bond to nitrogen is asymmetrically substituted (e.g., *D*-*sec*-butyl chloride $\rightarrow$ *L*-*sec*-butyltrimethylammonium chloride, Eq. 2).



The rate and position of equilibrium of such displacement reactions are known to be determined not only by the solvent, but also by the nucleophilicity (displacing power) of the amine, the stability of the leaving group, and the steric environment at the reaction site. A general discussion of the principles of displacement reactions would be inappropriate here, and it is assumed that the reader is familiar with them.

Since the stability of the leaving group is measurable by the strength of its conjugate acid, alkyl derivatives of all strong acids, such as alkyl halides, sulfates, benzenesulfonates, etc., are reactive alkylating agents; in practice, however, alkyl halides are used far more than all others.

The nature of the leaving group may also influence an important side reaction, elimination of HX from the alkylating agent to form an olefin (Eq. 3). Although this is not likely to be a significant reaction with pri-



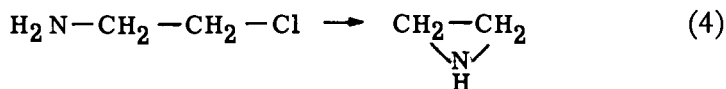
mary, saturated alkylating agents, it may assume major proportions when the structure is favorable, such as in β -phenylethyl and cyclohexyl halides. It has been found ^{12c,d} that toluenesulfonates are much less susceptible than are halides to base-catalyzed elimination by alkoxides, and they may behave similarly toward amines.

Amines themselves are poor leaving groups (their conjugate acids, R_3NH^+ , are weak), and halide ions are weak nucleophiles, so the alkylation reactions are effectively irreversible under ordinary conditions. The reverse reaction can be forced, however, particularly with quaternary amines, as will be discussed later.

Among amines, nucleophilicity is proportional to base strength, so that secondary amines might be expected to be the most rapidly alkylated. Steric interference effectively counteracts this effect with all but the smallest alkyl groups, however, and branched-chain secondary amines, such as di-*sec*-butylamine, $(\text{EtMeCH})_2\text{NH}$, may be very sluggish indeed toward further alkylation, especially by bulky alkylating agents. Tertiary alkylating agents, such as the *tert*-butyl halides, are so resistant to displacement reactions that alkylation of ammonia or amines by them is quite ineffective. Instead, elimination of HX catalyzed by the amine is virtually the sole reaction. Both *tert*-butylamine and di-*tert*-butylamine are made by methods other than alkylation, and tri-*tert*-butylamine, for which no other method has been developed, remains unknown.

Self-alkylation is obviously possible whenever an alkylating function is present in the same molecule with a primary, secondary, or tertiary amino group; it may occur internally to form a ring, or intermolecularly, to form a polymer. Three-membered rings, ethylene imines (aziridines),

are readily formed from β -chloroethylamines, for example (Eq. 4). Amines

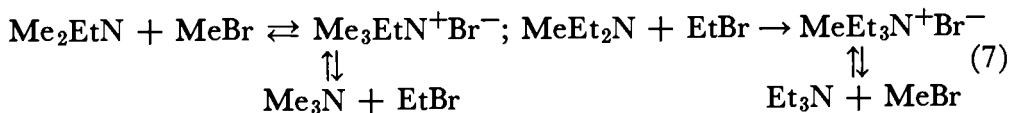
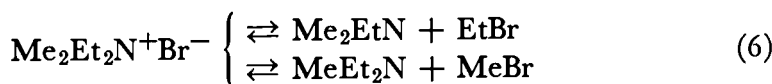


of this type are generally best handled as their salts, which, of course, are inert, no longer having a nucleophilic nitrogen.

When alkylation is easy, as in the reaction of ammonia or primary amines with primary alkyl halides, it is often a difficult problem to confine the reaction to mono alkylation. Various devices have been developed to meet this difficulty, in the form of reaction schemes to be discussed presently. When the opposite problem arises, usually with branched alkylating agents such as the isobutyl halides, it is preferred to use the more reactive iodide. It may not be necessary to prepare the alkyl iodide separately; a small amount of potassium iodide added to the reaction mixture is often an effective catalyst, acting through halide exchange. Although higher reaction temperatures and longer reaction times would appear to be obvious expedients, their excessive use may bring about difficulties of another sort.¹³ The ordinarily negligible reversal of the alkylation reaction (Eq. 5) may come into play. Unless all the alkyl



groups are the same, the alkyl groups are gradually redistributed, eventually in a statistical pattern, among all possible combinations, through a cascade of alkylations and their reversal. As a simple example, diethyldimethylammonium bromide may dissociate either to dimethylethylamine and ethyl bromide, or to diethylmethylamine and methyl bromide; recombination will then occur nearly at random to produce quaternary amines not originally present, and so on (Eqs. 6, 7). Redistribution

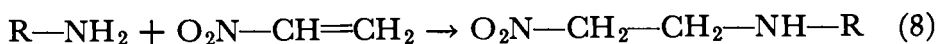


of alkyl groups is thus effectively catalyzed by heating an amine with small amounts of a quaternary ammonium salt.

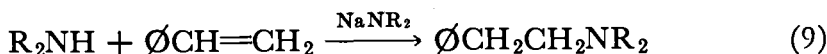
Commercially, alkylation of ammonia or amines is accomplished at higher temperatures with alcohols or olefins in the presence of surface catalysts composed largely of alumina or silica. It is a somewhat indiscriminate sort of process, but by empirical means can be controlled to give substantial amounts of specific amines.

OLEFINS AND ACETYLENES Most olefins are inert toward amines under

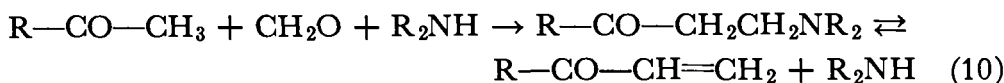
conventional conditions, but strongly electron-withdrawing substituents, which promote the attack of nucleophiles in general on olefins, enable a carbon-carbon double bond to function as an alkylating agent.^{14a,b} This behavior is met mostly in α,β -unsaturated nitriles (see Chapter 5), carbonyl compounds, and nitro alkanes (Eq. 8), but even styrene will add



amines under catalysis by sodium amides ^{14c} (Eq. 9). Olefinic alkylation

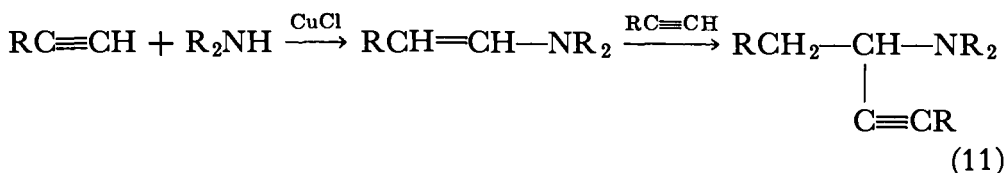


is often easily reversible; as a result, β -amino ketones, often called "Mannich bases" because of their easy formation by the Mannich reaction (see ahead) between an amine, formaldehyde, and a ketone, are sometimes useful sources of α,β -unsaturated ketones (Eq. 10).



Terminal acetylenes react with amines in a 2:1 ratio to give substituted propargylamines.^{14d} The reaction occurs in two steps, the first being

addition of $\begin{array}{c} \diagup \\ N-H \\ \diagdown \end{array}$ to the triple bond to give an enamine, followed by 1,2-addition of $RC\equiv C-H$ to the enamine double bond (cf. Chapter 7) (Eq. 11).



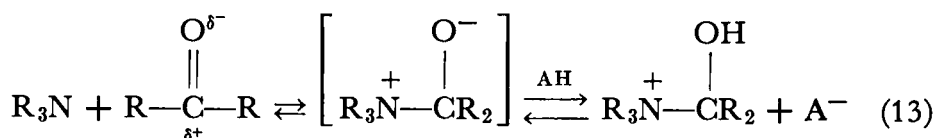
AMINATION Amination of amines can occur with reagents analogous to alkylating agents, although such reactions have not seen wide use. Both chloramine and its sulfate analogue, hydroxylamine-O-sulfonic acid, serve to aminate primary, secondary, and tertiary amines to hydrazine derivatives (see Chapter 9) (Eq. 12). The reactions appear to be nucleo-



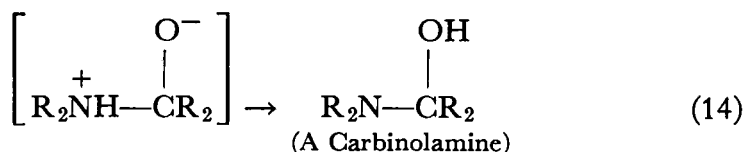
philic displacements on nitrogen, although there is a possibility that the reactive fragment, NH , may be the active agent under some circumstances.

ALDEHYDES AND KETONES The same nucleophilic properties of amines that are responsible for their reaction with alkylating agents enable them to attack the carbonyl carbons of aldehydes and ketones, relatively positive sites.¹⁵ The initial product of bond formation between carbon and nitro-

gen would be a zwitterion; since the negative charge is borne on an "alcoholic" oxygen, this species would be expected to be of somewhat high energy, and should dissociate readily into its components if no other reaction intervenes (Eq. 13). It may, however, acquire a proton from

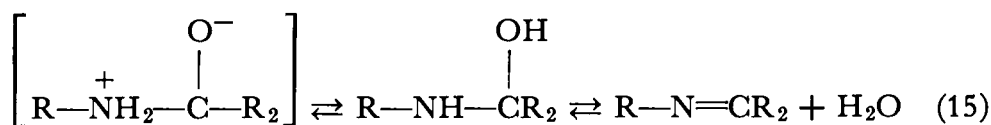


the solvent, especially if a weak acid is present, although the resulting compounds remain easily dissociable. When the amine is primary or secondary, the charge separation can be easily dissipated by proton transfer, giving rise to a class of compounds commonly known as "carbinolamines" (Eq. 14). They are not often stable enough to isolate (see Chap-

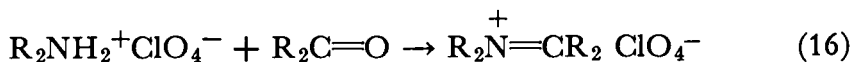


ter 7). They form most readily from aldehydes, and most difficultly from aromatic ketones; formaldehyde reacts with secondary amines to give almost entirely *gem*-diamine, $\text{R}_2\text{N}-\text{CH}_2-\text{NR}_2$.^{16c}

Carbinolamines derived from primary amines dehydrate readily; the reaction is acid-catalyzed, and may occur so readily that the carbinolamine cannot be isolated (Eq. 15). The aldimines and ketimines ("Schiff's bases") produced by this process will be discussed in Chapter 7. With secondary amines, ternary immonium salts are formed, often spon-

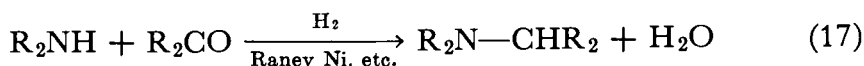


taneously, from both aldehydes and ketones ^{16d} (Eq. 16).

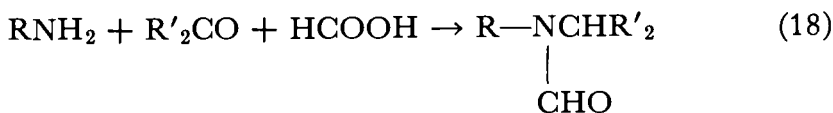


An important practical use of the reaction of primary and secondary amines with aldehydes and ketones is the synthetic process known as reductive alkylation.¹⁶ The reaction mixture of a primary or secondary amine with an aldehyde or ketone is treated with hydrogen in the presence of a hydrogenation catalyst; if the conditions are suitably chosen, very little of the carbonyl compound is reduced to alcohol, and reduction occurs instead on the products of reaction between the amine and the carbonyl

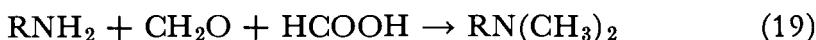
compound. The result is the addition of a new alkyl substituent onto the amine, derived from the aldehyde or ketone used (Eq. 17).



Reductive alkylation may also be carried out with formic acid (or derivatives) as the reducing agent, usually at about 150°, and is then known as the Leuckart reaction ^{61b} (Eq. 18). It is successful with am-

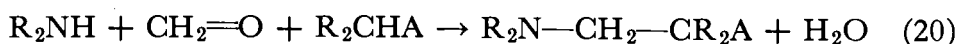


monia, primary and secondary amines, and although the yields are often moderate, its simplicity and cheapness still make it a useful synthetic method. The products from primary amines are actually formamides, except in the special case of alkylation with formaldehyde, which almost always introduces two methyl groups (Eq. 19). This process is often



referred to as the Eschweiler-Clark methylation.^{16b} Some interesting studies of the mechanism of the Leuckart reaction have been made, and it has been proposed that it proceeds by free-radical decarbonylation of an intermediate α -aminoalkyl formate, H_2N-CR_2-OCHO .^{16c}

Also of great practical importance in synthesis is the Mannich reaction, in which a primary or secondary amine reacts with an aldehyde (usually formaldehyde) in the presence of a third substance having an active hydrogen (e.g., ketones, nitro alkanes, malonic esters) (Eq. 20). The



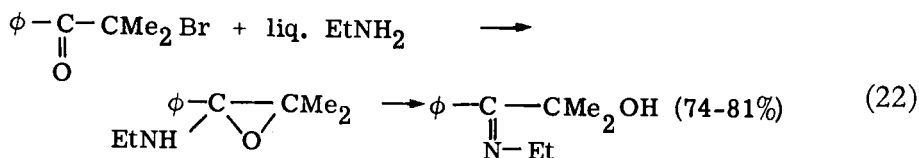
carbinolamine or its dehydration product, the aldimmonium ion, condenses aldol-fashion with the active hydrogen compound to form a new carbon-carbon bond as well as a carbon-nitrogen bond. The reaction rate is third-order, and has a maximum at pH 3.8; there is convincing evidence that the first step is reaction of amine with formaldehyde.¹⁷ Since the product itself may still have active hydrogens, further reaction can occur to produce di- or triamines. Amines with carbonyl or nitro groups in the β -position, such as are produced in the Mannich reaction, undergo ready elimination of amine, leaving α,β -unsaturated compounds (Eq. 21). An enormous variety of applications of the Mannich reaction



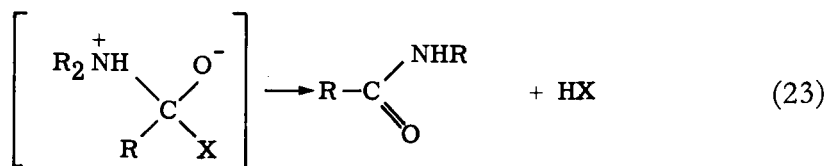
has been recorded.¹⁷

The reactions of primary amines with α -bromo ketones are of special

interest; the products may be α - or β -amino ketones, α,β -unsaturated ketones, or α -hydroxy ketimines.¹⁸ The last apparently arise from epoxy amines (Eq. 22).



ACYLATION Amines can react with the carbonyl portion of a carboxyl derivative in the same initial manner as they do with aldehydes and ketones. A new path for stabilization of the hypothetical intermediate zwitterion is available, however—separation of an anion from the carbonyl carbon (or the equivalent elimination process) (Eq. 23).



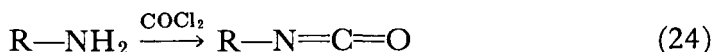
Salt-like addition products have been isolated from the reaction of tertiary amines with acid chlorides. Further reaction leads to conventional amides when the amine is primary or secondary, for a proton can then be lost as well.

The success of this reaction depends on the ease with which the initial addition takes place, and thus can be expected to vary with the basic strength of the amine, the reactivity of the carbonyl group, and the degree of steric interference that may develop as the substituents on the amine approach those on the carbonyl group. The familiar order of reactivity of carboxyl derivatives, $\text{R}-\text{CO}-\text{Cl} > (\text{R}-\text{CO})_2\text{O} > \text{R}-\text{CO}-\text{OC}_2\text{H}_5 > \text{R}-\text{CO}-\text{NH}_2 > \text{R}-\text{COO}^-$, reflects the influence of the eventual leaving group on the electrical state of the carbonyl carbon. Acid chlorides are usually violently reactive toward most amines, and at the other end of the scale, amine salts of carboxylic acids must usually be distilled to bring about conversion to amides.

The reaction of esters with amines has been the most extensively studied.¹⁹ Qualitatively, the importance of basicity is easily seen in the facts that straight-chain primary amines react faster than ammonia, and piperidine reacts faster than morpholine, a weaker base with the same steric requirements. The retarding effect of steric hindrance is seen in the facts that secondary amines react more slowly than ammonia, although they are stronger bases, and that esters of branched-chain alcohols or acids react more slowly than straight-chain esters. The kinetics of the reaction of amines with esters are somewhat complicated, however, and

two parallel paths of reaction appear to be involved. One is the reaction as we have so far considered it; the other is a base-catalyzed reaction, apparently involving the amide ion, R_2N^- , RNH^- , or NH_2^- . These anions are much more powerful nucleophiles, and react enormously faster than the corresponding neutral molecules. A consequence of this is that acylation of amines by esters is very effectively catalyzed by small amounts of sodium alkoxide, presumably owing to equilibria such as $RNH_2 + CH_3O^- \rightleftharpoons RNH^- + CH_3OH$.

The reaction of phosgene with secondary amines gives carbamoyl chlorides, $R_2N-COCl$, but with primary amines an elimination step follows very rapidly, producing isocyanates (see Chapter 6) (Eq. 24).



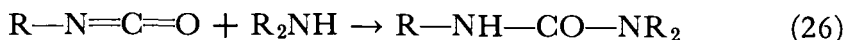
Acylation by other carboxyl derivatives is discussed in connection with the preparation of amides (Chapter 4).

Primary and secondary amines react with several types of compounds that can be considered as acylating agents even though they are not of the type $R-CO-X$. The simplest of these are perhaps the ketenes, $R_2C=C=O$. Addition of an amine across the $C-C$ double bond usually occurs spontaneously, producing amides uncontaminated with any other product (Eq. 25). It is not as useful a procedure as might be



supposed, however, owing to the difficulty in preparing most ketenes. On the other hand, ketene itself is readily prepared, and it has some use as a specialized acetylating agent.

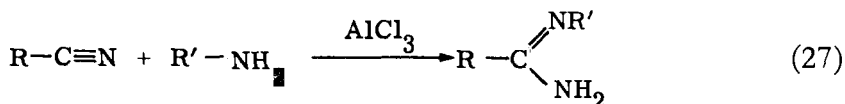
Isoelectronic with ketenes are isocyanates (and isothiocyanates), both of which react analogously, although not so vigorously. The products, of course, are ureas, which can also be looked upon as carbamoyl amides (Eq. 26). Isothiocyanates react more mildly than their oxygen counter-



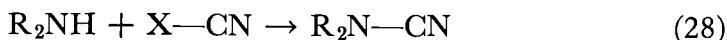
parts, and are often preferred for use in preparing crystalline derivatives of amines, because they do not react appreciably with water (isocyanates react rapidly with water to produce symmetrical ureas; see Chapter 6). The reaction of carbodiimides with amines to form guanidines also falls into this class (see Chapter 6).

Nitriles and imidate esters (imino esters), $R-C(=NH)OR'$, can be regarded as acylating agents of a sort, for they both react with amines to produce amides of imidic acids, commonly known as amidines (see Chapter 4). Ordinary nitriles are very sluggish toward this reaction, but catalysis by ammonium salts, or Lewis acids such as anhydrous aluminum

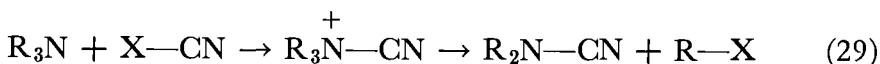
chloride (Eq. 27), is quite helpful.²⁰ With cyanogen halides, the acid



halides corresponding to cyanic acid, reaction is much more vigorous, resembling that of other acid halides; the products are cyanamides (Eq. 28), which may, however, react further to form guanidines. Ter-



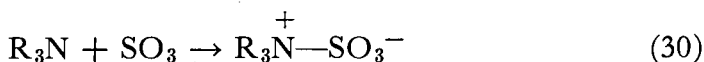
tiary amines undergo cleavage to alkyl and dialkyl-cyanamides (von Braun cleavage,²¹ see Chapter 6) (Eq. 29). This cleavage is appar-



ently a displacement reaction by halide on the most susceptible α -carbon. The displaced group, R_2NCN , is of very low basicity, and thus would be expected to be a reasonably good leaving group. Imidoyl esters are intermediate between nitriles and cyanogen halides in reactivity toward amines, and since they are relatively easily prepared from nitriles, are extensively used in amidine synthesis (see Chapters 4 and 5).

A number of inorganic acylating agents, mostly anhydrides, react with amines; the most important of these are the compounds of nitrogen and sulfur, and carbon dioxide.

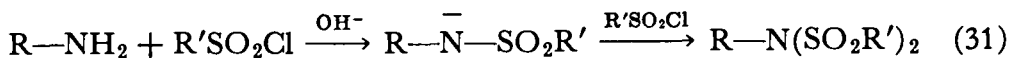
Sulfur trioxide reacts violently with amines, but when the reaction is moderated by passing vapor slowly into a solution of amine, sulfamic acid derivatives are formed.²² That is, the amine becomes sulfonated on nitrogen. With tertiary amines, this is the extent of the reaction, and the products are inner salts (Eq. 30). With primary and secondary



amines, such products are acidic, and combine with more amine to form ammonium sulfamates. Chlorosulfonic acid accomplishes the same reactions somewhat more conveniently. Sulfur dioxide behaves similarly, although not nearly so vigorously, producing thionamic acids, $\text{R}_2\text{NSO}_2\text{H}$, or their amine salts.²² This is analogous to the reaction of carbon dioxide with amines, which produces ammonium carbamates, $\text{R}_2\text{NCOO}^--\text{R}_2\text{NH}_2^+$. The rime that so often forms about the mouths of bottles of amines usually contains such salts formed from the carbon dioxide in the air. More about carbamate salts appears in Chapter 6.

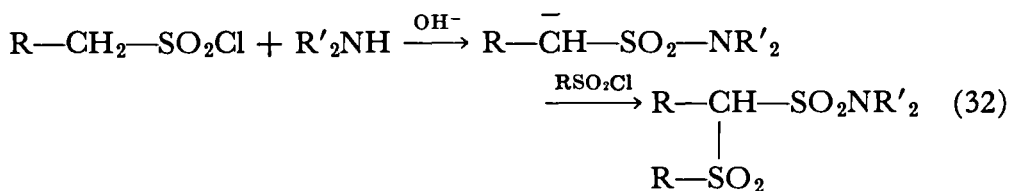
Sulfonyl chlorides acylate amines to form sulfonamides²³; this reaction is the basis of the familiar Hinsberg test for determining whether an amine is primary, secondary, or tertiary. Two significant side reactions are to

be noted.²³ Primary amines easily react with two moles of sulfonyl chloride, forming neutral sulfonimides (Eq. 31). This is a result of the



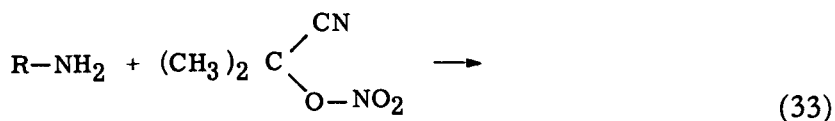
acidity of the initially formed sulfonamides, which exist largely as their anions in the strongly alkaline medium usually employed, and in that form can compete successfully with the amine for the remaining sulfonyl chloride. The other side reaction occurs with sulfonyl chlorides bearing α -hydrogens. The α -hydrogens of the corresponding amides are, of

course, acidic, and consequently give rise to some α -carbanion, $\text{R}-\text{CH}^--\text{SO}_2\text{NR}_2$, in alkaline media. Such carbanions are very reactive towards more sulfonyl chloride, and give rise to sulfones (Eq. 32), in some instances



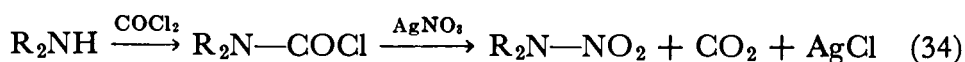
so readily that it is difficult to prepare a normal sulfonamide.

NITRATION Primary amines have not been successfully nitrated with nitric acid or N_2O_5 , apparently either because primary nitramines are too rapidly destroyed by the strong acid required, or because the amines are tied up too tightly as salts. Successful nitration has been accomplished, however, with α -cyanoisopropyl nitrate²⁴ (Eq. 33); in this reagent, the



leaving group in nucleophilic attack on the nitrate nitrogen would actually be two fragments, cyanide ion and acetone, considerably more stable than the simple alkoxide ion that would be the leaving group in nitration by ordinary alkyl nitrates. Secondary amines can be nitrated by 100% nitric acid if a small amount of chloride is also present as a catalyst.²⁵ The role of the catalyst appears to be to convert some amine to chloramine, which is then nitrated, accompanied by regeneration of positive chlorine for reaction with more amine. Alternative methods are the use of α -cyanosisopropyl nitrate, and the conversion to carbamyl chlorides by reaction with phosgene, followed by reaction with silver nitrate²⁶

(Eq. 34). Tertiary amines can also be nitrated; an alkyl group is removed



by nitrolysis in the process, and secondary nitramides are produced (Eq. 35). Such a process is presumably a step in the preparation of tetryl,



2,4,6,N-tetranitro-N-methylaniline, from dimethylaniline.

NITROSATION Nitrosation of amines is a far more involved subject than other types of inorganic acylation. The over-all picture is deceptively simple: tertiary amines are inert to nitrosation under ordinary mild conditions, secondary amines are converted to nitrosamines, R_2N-NO , and primary amines are deaminated with the production of nitrogen, alcohols, and olefins. The commonly used nitrosating agent is aqueous nitrous acid, which is actually an equilibrium mixture of several species²⁷; nitrogen sesquioxide ("nitrous fumes"), N_2O_3 , nitrogen tetroxide, N_2O_4 , and nitrosyl chloride, $ON-Cl$, can also be used, but the results are not necessarily the same.

The nitrosation of secondary amines to nitrosamines appears to be nearly free of complications, but it is not certain which species is the actual nitrosating agent when aqueous nitrous acid is used. The reaction proceeds easily at room temperature in dilute acid, and the products usually separate from the solution as they are formed, since they are no longer basic. It is a reversible reaction, and the nitrosamines can usually be hydrolyzed back to the original amine, much as other amides can.

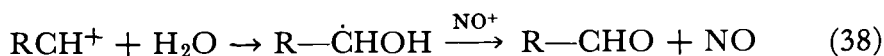
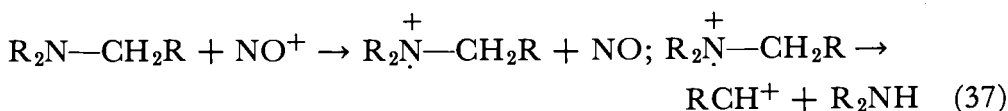
Although tertiary amines are ordinarily considered to be inert to nitrosation, and indeed, qualitative tests are based on this assumption, it was reported as long ago as 1864²⁸ that reaction will occur readily if the acidity of the medium is not too high, an alkyl group being cleaved from nitrogen. The products obtained are actually nitrosamines, resulting from subsequent reaction with more nitrous acid, and aldehydes or ketones (Eq. 36). Smaller alkyl groups are eliminated more readily than



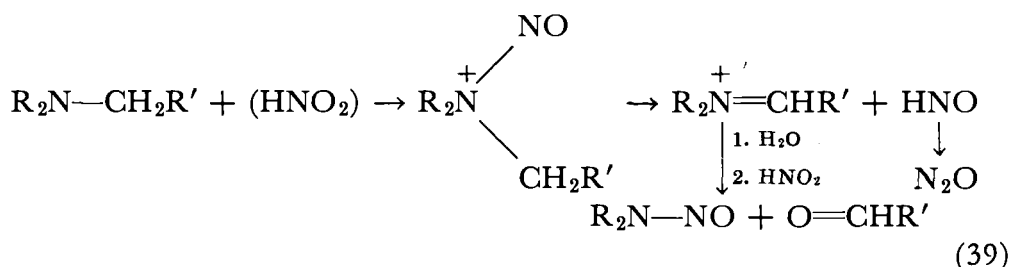
large ones, and benzyl is cleaved off particularly easily. Substituents of widely differing electronic character have only a small effect on the ease of removal of a benzyl group from an unsymmetrical tribenzylamine; *p*-methoxy favors removal, and *p*-nitro disfavors, with the Hammett constant, ρ , = -0.4, but amines that are weak bases are attacked more slowly than stronger ones. Tetranitromethane reacts with tertiary amines as a nitrosating agent and similarly accomplishes cleavage.

The mechanism has been considered from three different viewpoints ²⁹: as an oxidation of an α -carbon to give a hydrolyzable carbinolamine; as a free-radical cleavage of an initially formed nitrosammonium ion,

$\text{ON}-\overset{+}{\text{N}}\text{R}_3$, to give a radical ion, followed by further cleavage and redox reactions (Eqs. 37, 38); and as an elimination reaction of a nitrosam-

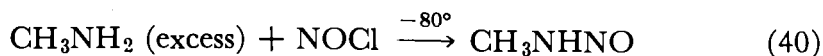


monium ion to form a hydrolyzable dialkylimmonium ion $\text{R}_2\overset{+}{\text{N}}=\text{CR}'_2$. The last process would require that nitroxyl, HNO , be the eliminated species, which would lead to formation of half a mole of nitrous oxide (see Chapter 1) (Eq. 39). The identification of nitrous oxide in approxi-

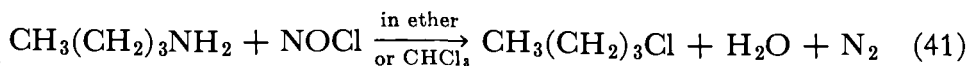


mately this proportion lends support to this path. The inertness of tertiary amines in strongly acidic solutions appears to result from retardation of an inherently slow reaction by severely lowering the concentration of free base, the species initially attacked.

Primary amines react with all varieties of nitrosating agents, usually to give mixtures of products complicated by the incursion of rearrangement of the Wagner-Meerwein type (see below). Nitrosyl chloride gives the simplest transformation; at very low temperatures, unstable primary nitrosamines are formed ^{30a} (Eq. 40), but otherwise this reagent replaces



an amino group by chloride in moderate yields. ^{30b,c} Isomerization does not usually occur significantly with this reagent; for example, *n*-butylamine gives *n*-butyl chloride (Eq. 41), and optically active α -phenylethylamine

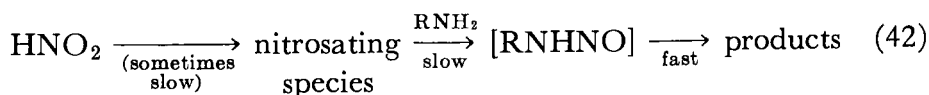


gives α -phenylethyl chloride with some retention of configuration. On the other hand, the products are always accompanied by other substances, often colored; they are apparently nitroso compounds derived from addition of nitrosyl chloride or oxides of nitrogen to olefins formed from the amine in a competing reaction, and from nitrosation of secondary amine formed by interaction of alkyl halide with primary amine. The products obtained cannot be attributed solely to the action of nitrosyl chloride, since water is produced, which hydrolyzes some nitrosyl chloride to oxides of nitrogen and hydrogen chloride.

The frequent absence of rearrangement in the reaction of nitrosyl chloride with amines shows that free carbonium ions may not be important intermediates. If the first step is the reasonable one of acylation, giving $R-NH-NO$, it must be followed by reaction with hydrogen chloride and/or more nitrosyl chloride to give an alkanediazo chloride, $R-N=N-Cl$, or the corresponding ion pair, $R-N_2^+Cl^-$. Conversion of this to alkyl chloride may be an intramolecular process, involving a frontal attack of the chlorine on the alkyl group, through a cyclic transition state, but unambiguous evidence is not yet available. Conversion to alkyl chlorides can also be brought about by treating an amine with a mixture of concentrated hydrochloric and nitric acids,³¹ a recognized source of nitrosyl chloride.

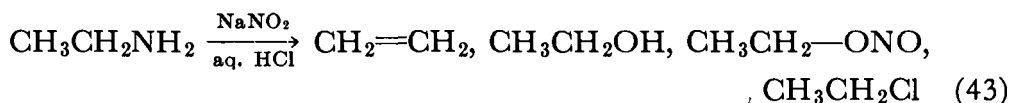
Most of the work on the nitrosation of primary amines has been done with nitrous acid generated from a nitrite salt and a strong acid in aqueous or acetic acid solution. The complexity of such reagents became slowly apparent as kinetic studies of nitrosation and diazotization were pursued.²⁷ Not only are molecular nitrous acid, HNO_2 , and its anhydride, N_2O_3 , present, but also nitrous acidium ion, $H_2NO_2^+$, nitrosyl cation (nitrosonium ion), NO^+ , and nitrosyl compounds, $X-NO$, derived from other anions present. Since all of these species are capable of nitrosating an amino group to a greater or lesser degree, the rate equations are usually complex, unless limiting conditions are used such that only one nitrosating agent dominates. The rate is thus dependent on the other anions in solution—chloride, acetate, etc.—and the reaction can be considered to be catalyzed by such anions in many cases. Failure to recognize this caused frustrating discrepancies among earlier investigations, which were not resolved until the last decade.³²

The rate-determining step varies with conditions, being either the formation of an active nitrosating species (e.g., the formation of N_2O_3 from HNO_2), or nitrosation of the amino group (Eq. 42). It is the free

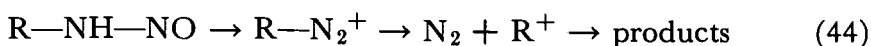


amine, and not the cation, that is attacked. Because of this, the reaction may be retarded or even prevented by too high an acidity of the medium, and the practical limit for aliphatic amines is about pH 3; on the other hand, higher acidities favor the formation of more active nitrosating species. All kinetic evidence so far reported indicates that the steps leading from the primary nitrosamine to products are much faster than the preceding stages.

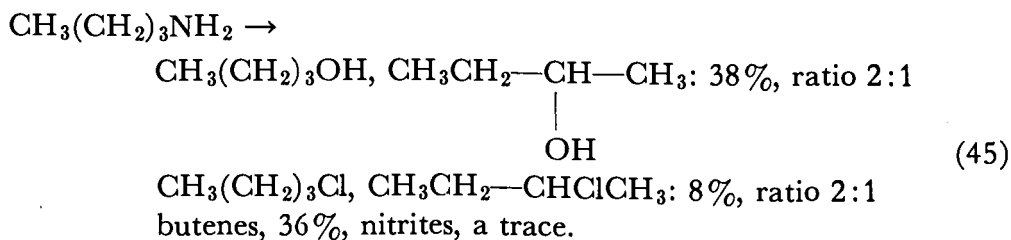
The products formed from nitrosation of a primary amine depend on the experimental conditions, but in general they consist of mixtures of isomeric olefins and cyclopropanes, isomeric alcohols, and isomeric alkyl derivatives of the various anions that may have been present. It should be clear at once that the reaction is seldom of preparative value, although its theoretical interest is very great. Let us first consider for simplicity a case where isomerization is not possible, such as ethylamine. The principal products are ethylene and ethyl alcohol, but if the nitrous acid is generated from sodium nitrite and hydrochloric acid, ethyl nitrite and ethyl chloride may be expected as well (Eq. 43).



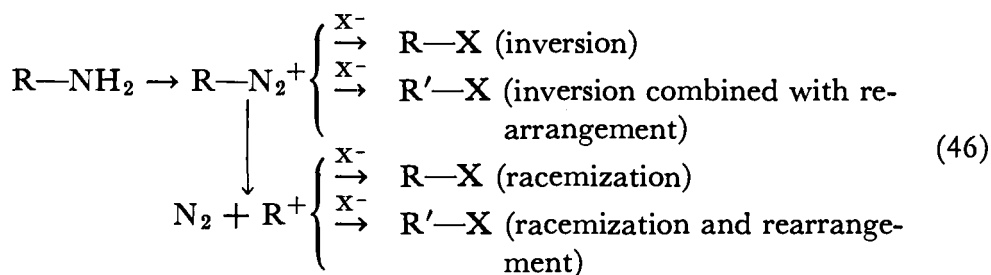
The Whitmore hypothesis of the intermediate formation of a carbonium ion, in this case C_2H_5^+ , as the common precursor of all the observed products, was advanced in the 1930's to correlate the observations. According to this, the primary nitrosamine is rapidly dehydrated in acidic solution to an unstable diazonium ion, which in turn rapidly loses nitrogen (Eq. 44). This plausible explanation had the advantage



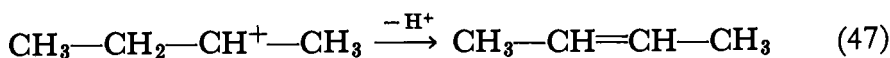
of predicting that isomerism (Wagner-Meerwein rearrangement) would occur with alkyl groups of suitable structure, according to a pattern that had been observed for otherwise unrelated reactions, such as Friedel-Crafts alkylation. The prediction had pronounced qualitative success, as shown by the example of *n*-butylamine,³³ which was found to give the same sorts of products as ethylamine, except that each type of product was a mixture of isomers resulting from hydrogen migration (Eq. 45) (examples of carbon-skeleton isomerization will be discussed further on).



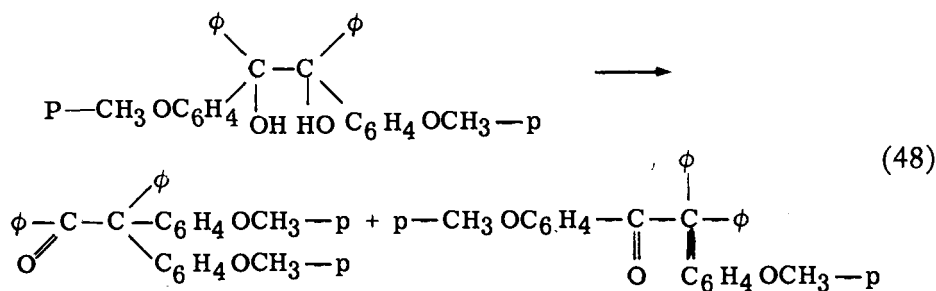
The simple carbonium theory met certain difficulties when stereochemical evidence was obtained and when quantitative comparisons were made. Carbonium ions should give rise to racemic products whenever the site of optical asymmetry becomes a tricoordinate carbon, such as would be expected with *sec*-butylamine. With this and related compounds it was found that a considerable amount of inversion of configuration actually occurred. Such observations led to the modified concept that nitrogen might actually be displaced from a diazonium ion by the solvent or other nucleophilic species, thus giving rise to a product that did not come from a free carbonium ion. The formation of optically active yet rearranged products could be accommodated by this concept if it is assumed that rearrangement may be concerted with displacement of nitrogen in a sort of combined S_N2' - S_{Ni} process, in which the migrating group displaces the nitrogen while a nucleophile attacks the migration origin. We thus have a set of competing reaction paths, which may lead to products with or without rearrangement or racemization (Eq. 46).



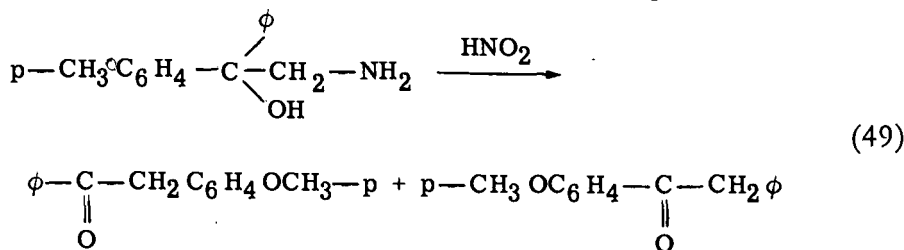
Such a flexible scheme would seem difficult to dislodge, but nevertheless, evidence accumulated that it was unsatisfactory. Certain amines were found to show a preference for *retention* of configuration, specifically α -phenyl-*sec*-butylamine and amines of equatorial conformation, such as the *cis*-decalylamines and *cis*-cyclohexylamine-2-d.³⁴ Furthermore, significant differences were noticed between the products presumed to be produced from carbonium ions formed from amines and nitrous acid, and those found in certain other reactions, such as solvolysis of sulfonate esters.³⁵ For example, considerable amounts of butene-2 are obtained both from solvolysis of *sec*-butyl toluenesulfonate and from nitrosation of *sec*-butylamine, but the ratios of stereo-isomers are quite different; the butene from solvolysis consists of *cis* and *trans* isomers in the ratio 1:1, whereas that from nitrosation has the ratio 2.9:1 (neither ratio is the equilibrium value). The olefins are presumed to arise from an elimination in which *sec*-butyl cations are first formed, and then lose a proton (Eq. 47).



If the concept of carbonium ions as the precursors of the products from the various types of reaction is to be retained, one is forced to conclude that there can be more than one kind and state of carbonium ion. Such a conclusion has been reached by a number of investigators, who have assumed that the aliphatic diazonium ion is of such high potential energy that its decomposition produces a "hot" carbonium ion, of higher than usual potential energy.³⁶ The higher energy content is presumed to increase the reactivity of the species considerably, making it less selective among alternate paths of reaction, and more capable of inducing rearrangement within itself. This concept has the additional advantage of explaining the pronounced differences in migration aptitudes observed between deaminations and other reactions believed to involve carbonium ions. The *p*-methoxyphenyl group, for example, shows a very high migration aptitude in the pinacol rearrangement, 500 times that of phenyl (Eq. 48). In rearrangements accompanying deamination, how-



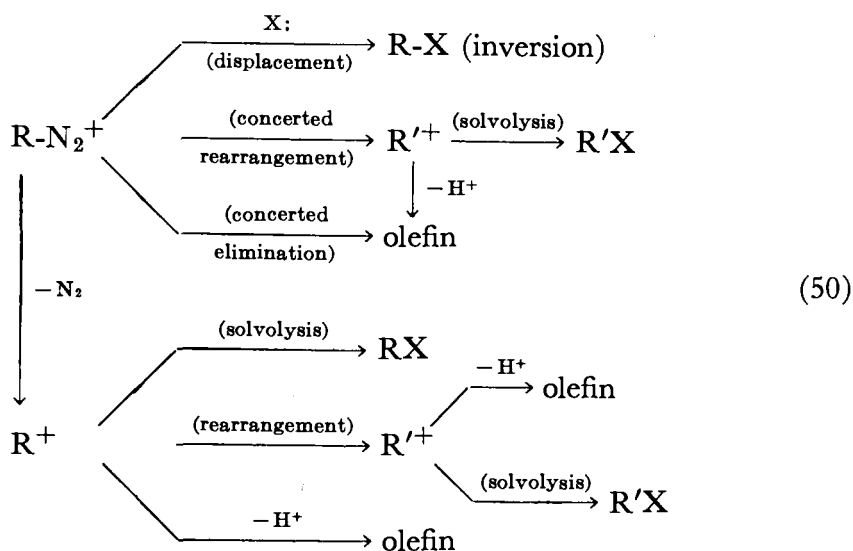
ever, *p*-methoxyphenyl migrates only slightly more readily than phenyl (Eq. 49). These facts are consistent with the concept that the "hot"



carbonium ion from the amine induces rearrangement so fast that little selectivity appears, and the ratio of migration is near the statistical.

Streitwieser has developed a comprehensive approach to the question of the nature of the deamination reaction^{35a,b} which does not require the concept of "hot" carbonium ions. He considers that only ordinary carbonium ions are produced, and that both rearrangement and elimination may be concerted with loss of nitrogen. This implies that one should look to the properties of the transition state of the step in which nitrogen is lost for the explanation of the special characteristics of the deamination reaction. The scheme of possible competing reactions is otherwise

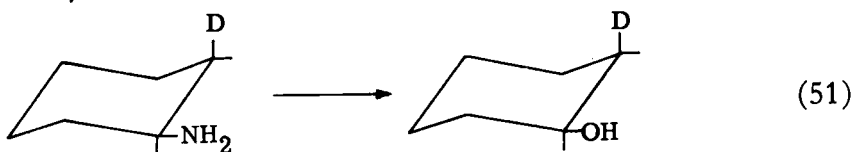
similar to the older one; the properties before attributed to a "hot" carbonium ion are now attributed to a diazonium ion (Eq. 50).



The key feature of the Streitwieser proposal is that it recognizes that the activation energy for the loss of nitrogen from an aliphatic diazonium ion by any process is probably very low, so that the absolute magnitude of differences in activation energy among the various pathways must all be small. That is, the range of activation energies is relatively compressed, and all pathways can therefore compete to a significant extent. In contrast, solvolysis of alkyl sulfonates, for example, has a much higher activation energy, and the differences among the various pathways would be expected to be correspondingly large. This leads to a pronounced selectivity in respect to the pathways followed, and most of the product is formed by the paths of lowest activation energy: solvolysis or elimination without rearrangement. This situation can be seen to be reasonable when it is considered that the relatively unstable diazonium ion must reach the transition state, the midpoint in its decomposition, when the nitrogen-to-carbon bond is only slightly stretched, but for alkyl sulfonates, the alkyl group must be considerably separated from the sulfonate moiety before the "downhill" stage to products is commenced. This situation holds alike for each of the pathways: displacement, elimination, rearrangement, and dissociation.

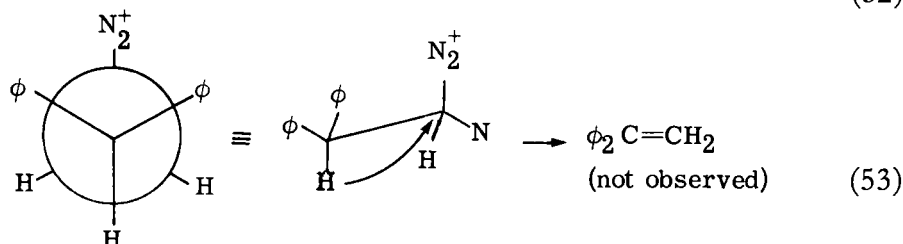
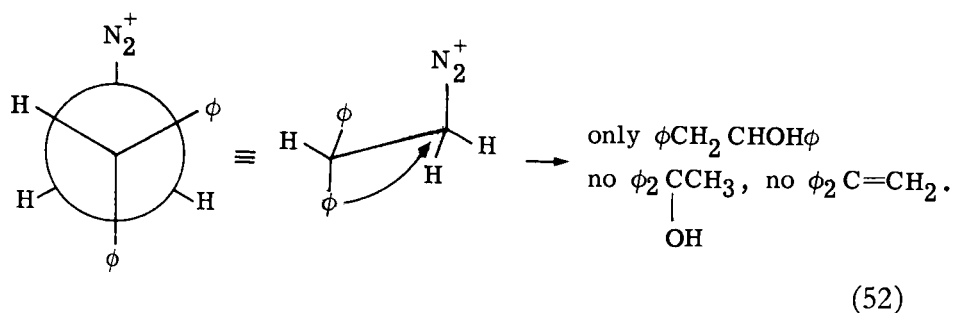
If the activation energy for decomposition of alkyl diazonium ions should be low enough, it would be similar to that for internal rotations about carbon-carbon single bonds (*ca.* 4 kcal/mole). This situation has the important consequence that decomposition can compete in speed with rotation within the molecule, and the nature of the products may then

be determined by the rotational position, the conformation, of the diazonium ion. For elimination, which proceeds far more readily when the fragments to be eliminated are *trans* to one another, the structure of the olefin will thus be largely determined, as well as the relative extent of elimination compared to competing reactions, by the rotational conformation of the amine (strictly, of the diazonium ion). For example, substituted cyclohexylamines having an amino group in an equatorial position, such as *cis*-cyclohexylamine-2-d, are known to give largely alcohol and very little olefin on treatment with nitrous acid ^{34b} (Eq. 51).



There are no hydrogens *trans* to an equatorial group, so this result is not surprising; elimination cannot compete for steric reasons. The alcohols formed are nearly always equatorial; that is, the configuration is retained. With axial amino groups, the opposite situation obtains; most of the product is olefin, and the alcohol formed is mostly inverted (equatorial). Now ordinary displacement reactions are known to be very slow with cyclohexyl compounds, so the absence of significant inversion, which would require a displacement path, is not unexpected. The possibility that the alcohols in these reactions are formed through dissociation of the diazonium ion to a carbonium ion, "hot" or normal, is unlikely in view of the high stereospecificity; a considerable amount of racemization would be expected. What remains is the concept of frontal attack, by the solvent or other nucleophile, perhaps through an intimate ion-pair or analogous solvate. Since there are other reactions that point strongly to carbonium ion intermediates in amine-nitrous acid reactions, it seems probable that the detailed path followed from reactants to products may vary, depending on both structure and experimental conditions. The question is open, pending further studies.

Rearrangement reactions that are concerted with a dissociation also have the steric requirement of a *trans* conformation for easiest reaction. If dissociation and the rearrangement that it induces are fast compared to internal rotation, the products will be largely determined by which group is in the most favorable position to migrate. For example, 2,2-diphenylethylamine (and the corresponding diazonium ion) would be expected on steric grounds to exist very largely in rotational conformations with the nitrogen turned away from the large phenyl groups and thus more or less *cis* to the β -hydrogen atom. In this position, the hydrogen cannot readily take part in either rearrangement or concerted elimination, and it is not surprising that neither 1,1-diphenylethanol nor 1,1-diphenylethylene is formed (Eqs. 52, 53). Isobutylamine has an

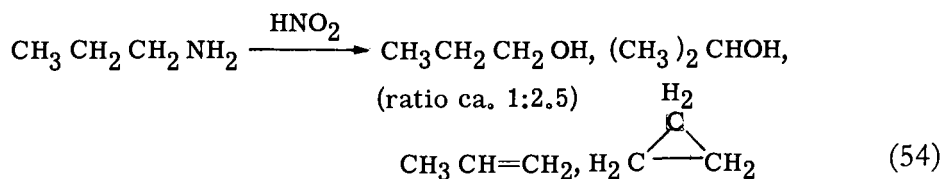


(optimum conformation for hydrogen migration, showing steric repulsion between N_2^+ and both phenyls).

analogous structure with the phenyl groups replaced by methyl, whose steric requirements are less. It is not so restricted in conformation, and methyl would not be expected to have as great an intrinsic migration aptitude as phenyl; accordingly, appreciable amounts of tertiary butyl alcohol are formed from it.

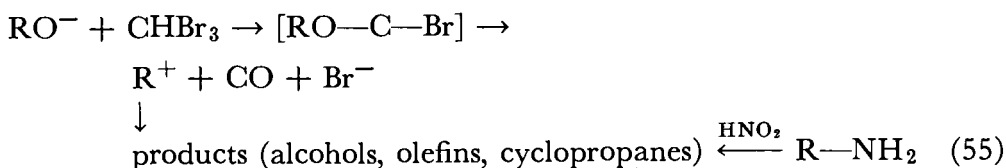
Similar reasoning can be used to understand why there is little selectivity in migrations among various *para*-substituted phenyl groups; although the electrical differences, and thus the intrinsic migration aptitudes, vary widely, steric requirements are essentially identical, and one aryl group is as likely to be in a position to migrate as the next. The depressed migration aptitude of *p*-methoxyphenyl groups in deamination reactions, referred to in a previous paragraph, can thus be explained by this concept as well as by the concept of "hot" carbonium ions.

It is in order to consider from a descriptive viewpoint some of the more important rearrangements accompanying deamination. Although the reaction of aliphatic primary amines with nitrous acid nearly always gives appreciable amounts of "olefin," commonly of the order of 30%, it was only in 1960 that Skell and Silver independently discovered that the olefin fraction consists in some cases largely of a cyclopropane^{35c, 37} (Eq. 54). It is difficult to formulate the production of such compounds



except as an internal electrophilic attack at a saturated carbon of a carbonium ion. It is significant that the same products are obtained in reac-

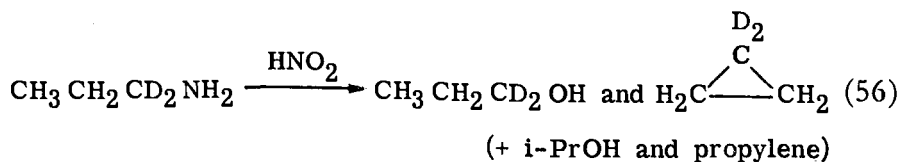
tions that generate carbonium ions in an entirely different way, such as the deoxidation of alkoxide ions by bromoform (Eq. 55).



It is the alcohols that have been most thoroughly investigated. The simplest case, ethylamine $\rightarrow$ ethanol, is in principle capable of rearrangement, but the result is only detectable with the help of isotopic tagging. Such an experiment with ethylamine-1- C^{11} produced almost solely ethanol-1- C^{11} , thus showing the absence of rearrangement.³⁸ There is, of course, no driving force for rearrangement in such a case, since the product of rearrangement would be energetically no different from that from loss of nitrogen without rearrangement. That significant equilibration did not take place is taken to mean that a bridged cation (ethylene with a protonated double bond) is of considerably higher energy, for it should otherwise provide a path for equilibration.

n-Propylamine gives more than twice as much isopropyl alcohol as *n*-propyl alcohol, but as the chain length of *n*-alkylamines is increased, the extent of isomerization decreases, leveling off at about 70% unrearranged primary alcohol.

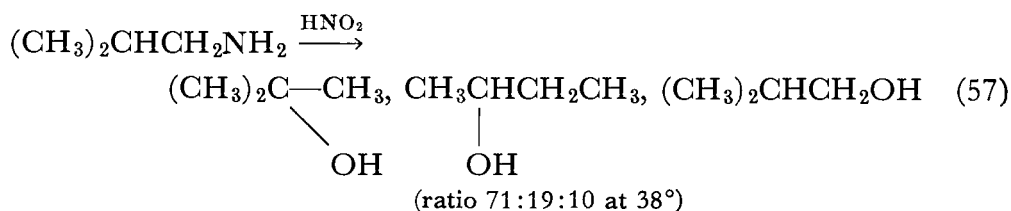
The secondary alcohol must result from hydrogen migration, of course, since migration of an alkyl group would only give primary alcohol indistinguishable from that arising without rearrangement unless isotopic labeling is used. This subject has been investigated both with $\text{CH}_3\text{-CH}_2^{14}\text{CH}_2\text{NH}_2$ (carbon labeling)³⁹ and $\text{CH}_3\text{CD}_2\text{CD}_2\text{NH}_2$ (deuterium labeling).⁴⁰ In neither case could any of the product to be expected of methyl migration be detected; however, in both cases, about 10% of the *n*-propyl alcohol produced had isotope distribution corresponding to a 1,3 shift of hydrogen. On the other hand, β -cyclopropylethylamine-1- C^{14} undergoes a considerable amount of migration of the cyclopropyl group to C-1.⁴¹ The possibility of carbene intermediates has been entertained, but since neither the *n*-propyl alcohol nor the cyclopropane³⁷ obtained from α -di-deuterated propylamines shows loss of the deuterium, carbenes cannot play a significant role (Eq. 56). The same evidence eliminates



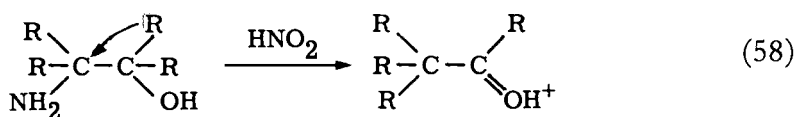
the possibility of the intermediacy of 1-diazopropane, $\text{CH}_3\text{CH}_2\text{CH}=\text{N}_2$. The subject is intimately bound up with the larger one of the nature and

behavior of carbonium ions in general, which at the time of writing is in a fluid state, rapidly changing.

Isobutylamine is an interesting case, because both hydrogen migration and methyl migration are promoted by the generation of a more stable carbonium ion, tertiary in the first case, secondary in the latter. The alcohol produced is largely *tert*-butyl, resulting from hydrogen migration and accompanied by the greatest stabilization, but a significant amount of *sec*-butyl alcohol is produced as well ⁴² (Eq. 57).

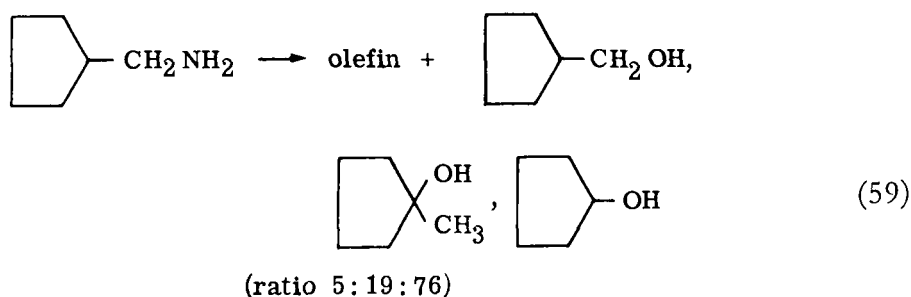


When a hydroxyl group is on the carbon adjacent to that bearing the amino group, an even greater driving force for rearrangement is present, for the result can be the conjugate acid of a carbonyl compound, a much more stable species than even a tertiary carbonium ion (Eq. 58). Such



a rearrangement bears a close relationship to the pinacol rearrangement, and is called semipinacolic deamination. When it is structurally possible, it usually occurs to the near exclusion of other reactions. Examples of it have been mentioned in previous paragraphs.

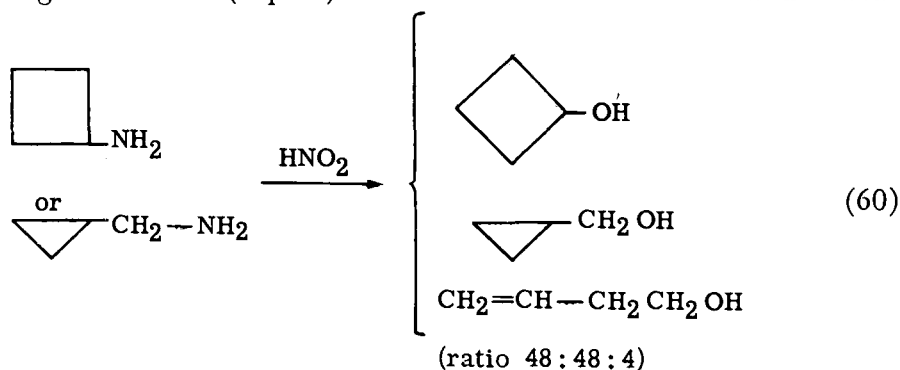
Cyclic compounds bring in yet other factors, particularly conformation and ring strain. Rearrangements of aminomethylcycloalkanes were first studied by N. Demyanov (Demjanow), and are usually referred to as Demyanov rearrangements.⁴³ There has been some tendency to call all deaminative rearrangements Demyanov rearrangements. The earliest example is typical; aminomethylcyclobutane gives largely cyclopentanol. Aminomethylcyclopentane has been more thoroughly investigated, and although ring expansion predominates, hydrogen migration is also appreciable, and some unrearranged alcohol is produced as well ³⁰ (Eq. 59).



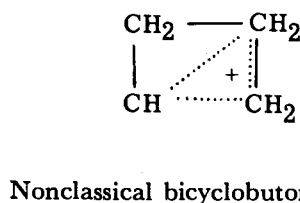
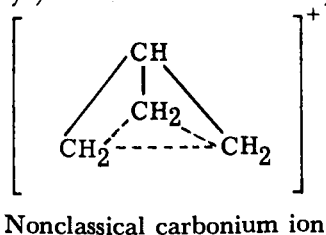
The situation is clearly different from isobutylamine. The relief of a small amount of ring strain, which should promote expansion, and the increase of ring strain that would result by conversion of a tetrahedral carbon to a trigonal carbonium ion at position 1 if hydrogen migration occurred, are undoubtedly important in determining the observed result.

The extent of ring expansion falls as the ring size increases; aminomethylcyclohexane produces alcohols that contain only 63% of cycloheptanol, and the results from larger rings are worse. When the difficulty of separation of a given alcohol from the mixtures is considered, it can be seen that the Demyanov ring expansion is seldom of synthetic value.

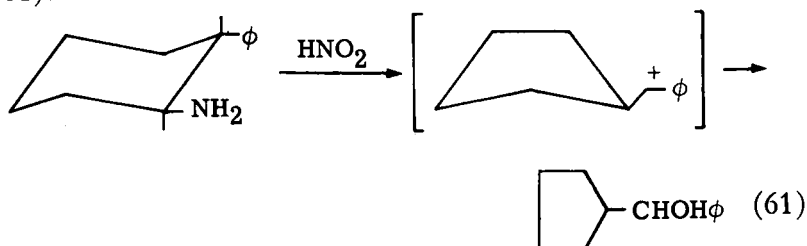
Four- and three-membered rings, with their considerable ring strain, would be expected to undergo Demyanov ring expansion to a very large extent. This expectation is borne out with four-membered rings, but the behavior of aminomethylcyclopropane is anomalous.⁴⁴ It gives a mixture of cyclobutanol and cyclopropylcarbinol in the same proportion as obtained from cyclobutylamine, which strangely enough undergoes partial ring contraction (Eq. 60). This behavior led Roberts and Mazur



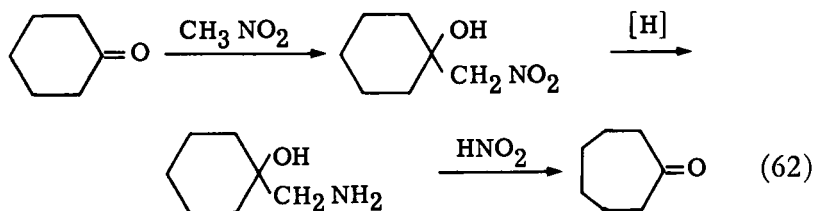
to propose as a common intermediate a "nonclassical" carbonium ion, whose solvolysis would produce the observed products. This proposal initially appeared to be supported by experiments with aminomethylcyclopropane isotopically labeled at the α -carbon; it was soon found⁴⁵ that the three methylene groups do not become entirely equivalent at any intermediate stage. The facts are presently believed to be explained by the formation of a rapidly equilibrating mixture of carbonium ions, which may be either classical (cyclobutyl, cyclopropylcarbinyl, allylcarbinyl) or nonclassical "bicyclobutonium" ions, such as shown here.



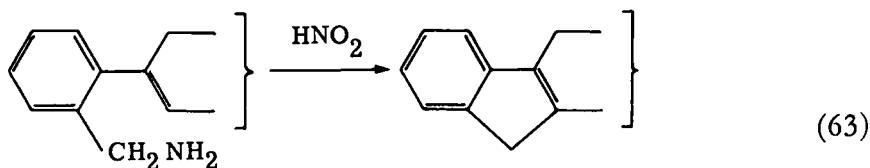
When the structural changes provide sufficient force, ring contraction may actually predominate. An example is *trans*-2-phenylcyclohexylamine. Although hydrogen migration would produce a very stable tertiary, benzylic carbonium ion, the configuration does not permit it (H is *cis* to $-N_2^+$); instead, migration of a ring methylene occurs, giving a secondary, benzylic carbonium ion, which then gives phenylcyclopentylcarbinol (Eq. 61).



When semipinacolic deamination is applied to ring compounds, it can force ring expansion to occur in spite of otherwise unfavorable conditions. This application is known as the Tiffeneau-Demyanov ring expansion⁴⁴; since the yields are usually high and the product of uniform composition, it is a useful synthetic method. There are many ways of making the 1-aminomethylcycloalkanols, particularly from ketones, allowing the ring size to be expanded stepwise repeatedly (Eq. 62).



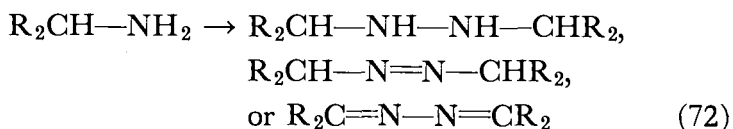
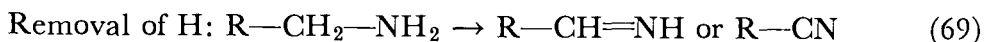
Yet another type of reaction of diazotized aliphatic amines is cyclization to form a new C—C bond; it has been observed only in special situations⁴⁶ (Eq. 63).



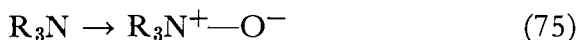
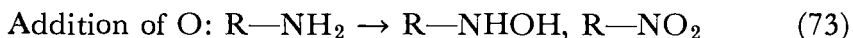
DIAZO COUPLING We may now proceed to the reactions of amines with some other electrophilic nitrogen compounds. The most important is the coupling of primary and secondary amines with aromatic diazonium salts, which gives triazenes, also called diazoamino compounds (Eq. 64).



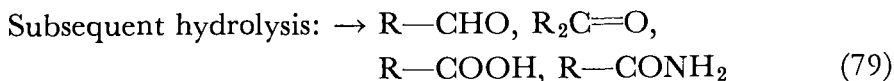
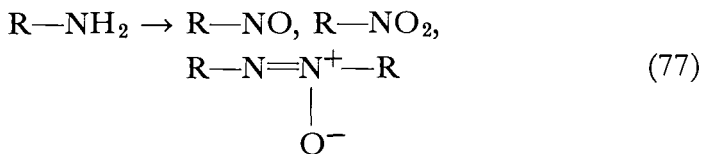
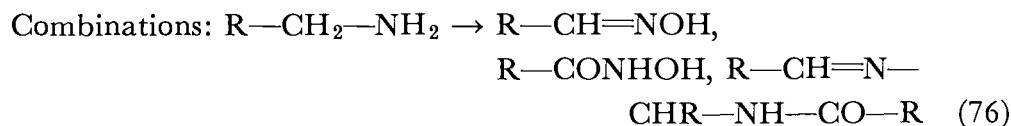
OXIDATION Oxidation of amines ⁵⁰ can follow a variety of courses, depending very much on the reagent as well as the structure of the amine. The products arise from the removal of hydrogen from one molecule to give aldimines, ketimines, enamines, or nitriles, or from two molecules to give hydrazines or azo compounds (Eqs. 69–72); the addition of oxygen,



to give hydroxylamines or amine oxides (Eqs. 73–75); or combinations of



these processes, to give nitroso, nitro, or azoxy compounds, oximes, hydroxamic acids, or the hydrolysis products of any of these substances (Eqs. 76–79).



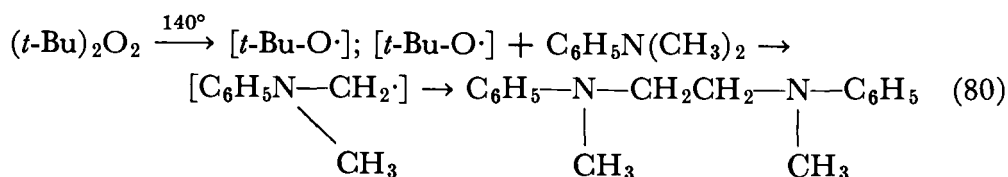
As a rough general rule, peroxy acids and hydroperoxides add oxygen to the nitrogen atom, and other types of oxidizing agents add oxygen to carbon and/or remove hydrogen. Both classes of oxidizing agents can act in both ways, however, and as the products obtained result from competitive reactions, there are many exceptions. Hydrogen is perhaps more

easily removed from an α -carbon than from a nitrogen, for amines bearing only tertiary alkyl groups appear to be a little more resistant to such reagents as permanganate and chromate than are other amines. In general, an amino nitrogen activates the α -hydrogens to oxidation much as do alcohol oxygens. The evidently complex subject of oxidation of amines has only recently begun to be investigated systematically.

Peroxide oxidations will be considered first. With tertiary amines, hydrogen peroxide and acyl peroxides usually do no more than add an

oxygen atom to nitrogen, giving amine oxides, $R_3\overset{+}{N}-O^-$ (see Chapter 8). The reaction is generally quite easy to carry out, and usually occurs when the reagents are allowed to stand in solution for a few hours.⁵⁰ At low temperatures and in concentrated solution, intermediate hydrogen-bonded adducts, $R_3N \cdot H_2O_2$, can be isolated.^{50b} Water and alcohol are convenient solvents to use with hydrogen peroxide, whereas benzene is suitable when benzoyl peroxide is used. The reaction is subject to steric interference, and amines not quaternizing readily are generally difficult to convert to amine oxides. Ozone also converts tertiary amines to N-oxides.^{53c}

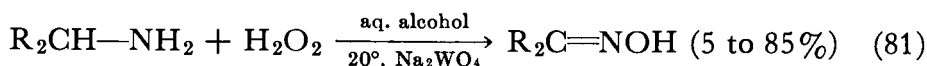
t-Butyl peroxide at a higher temperature affects tertiary amines in a quite different way, abstracting a hydrogen from an α -carbon and giving dimers, ethylenediamine derivatives.⁵¹ Dimethylaniline, for example, is converted to *N,N'*-dimethyl-*N,N'*-diphenylethylenediamine in 28% yield, presumably by a free-radical reaction starting with *tert*-butoxy radicals (Eq. 80).



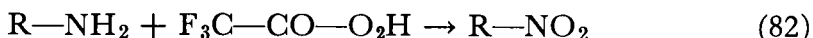
Secondary amines are for the most part easily converted to *N,N'*-dialkyl hydroxylamines by hydrogen peroxide, a reaction of considerable synthetic value^{50a} (see Chapter 8). It can be considered that a secondary amine oxide, $R_2NH^+-O^-$, is formed first, and rapidly tautomerizes. Although it is a general reaction, it fails with the simplest example, dimethylamine.

The oxidation of primary amines by hydrogen peroxide is complicated by the fact that there can be several stages, and a useful yield of any one product cannot usually be obtained. If the alkyl group is also primary, however, some hydroxamic acid, $R-CO-NHOH$, is always formed,^{52a} and since this structure can be detected quite sensitively by the wine-red complex formed with ferric chloride, the reaction is a useful test for the structure $R-CH_2-NH_2$. Secondary alkyl primary amines can be

converted to oximes in yields that may be quite good ^{52b} (Eq. 81). Peroxy-

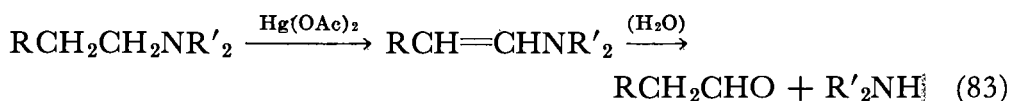


acetic and -trifluoroacetic acids convert amines to nitro compounds in moderate yields ^{52c,d} (Eq. 82); the reaction apparently involves nucleo-

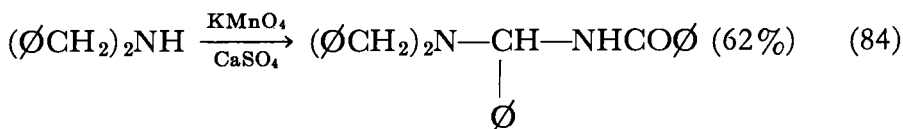


philic attack by the amine on the unsubstituted oxygen.

Other oxidizing agents, ⁵³ such as manganese dioxide, chlorine dioxide, permanganate, or mercuric acetate, attack the α -hydrogens of tertiary amines, giving vinylamines (enamines) or their hydrolysis or further oxidation products, and may thus accomplish oxidative cleavage of an alkyl group from nitrogen (Eq. 83). Secondary amines are oxidized



much as are tertiary amines, with the added factor of the formation of aldimines or ketimines by the removal of a hydrogen from nitrogen (or tautomerization of an initially formed vinylamine). The ease with which the imines react with more amine to give *gem*-diamine derivatives sometimes makes it difficult to obtain imines by oxidation ^{50c} (Eq. 84)

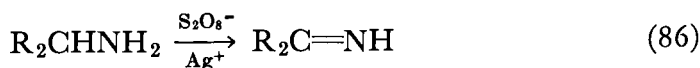


(but cf. oxidation of N-alkyl anilines, Chapter 3).

Oxidation of primary amines with reagents other than peroxides proceeds much as with secondary and tertiary amines. Although imines are presumably first formed in all cases, only their further reaction products are sometimes isolated. ^{53c, 54} When the alkyl group is primary, hypohalites remove four hydrogen atoms to produce nitriles (Eq. 85).

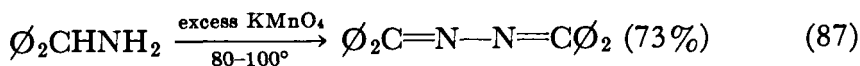


When the alkyl group is secondary, ketimines or their transformation products are formed ⁵⁴ (Eq. 86). The action of hot permanganate on

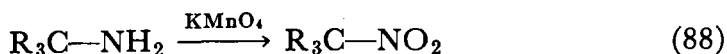


benzhydrylamine is exceptional in that N—N bond formation becomes

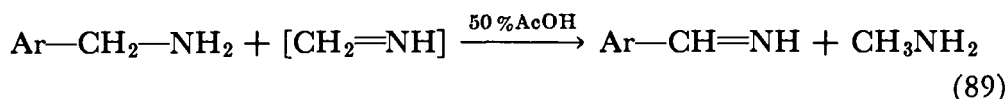
the major process, giving rise to benzophenone azine ^{53c} (Eq. 87). When the alkyl group is tertiary, there is no α -hydrogen to be attacked; oxidation



can occur readily only on nitrogen, to give products similar to those formed with peroxides. Thus *tert*-butylamine is oxidized to *tert*-nitrobutane in good yield by permanganate ⁵⁵ (Eq. 88).



SOMMELET REACTION The Sommelet reaction, principally used as a preparative method for aldehydes, is essentially a dehydrogenation of an amine to an aldimine. It occurs when primary alkyl halides, especially benzyl, are treated with hexamethylene tetramine ("hexamine") in a weakly acidic, hydrolyzing environment, and appears to involve hydrolysis of the initially formed N-alkyl quaternary salt to alkylamine and formalimine, which then exchange hydrogen (Eq. 89). An understand-



ing of these steps has enabled hexamine to become a useful reagent for the dehydrogenation of amines in general; the process is usually accompanied by hydrolysis of the imine, so that an aldehyde or ketone is actually produced.⁵⁶ Dehydrogenation has also been accomplished by heating amines with hydrogenation catalysts, such as nickel or platinum.⁵⁷ (Similar results have been achieved by treating amines with halogens or hypohalites—see ahead.)

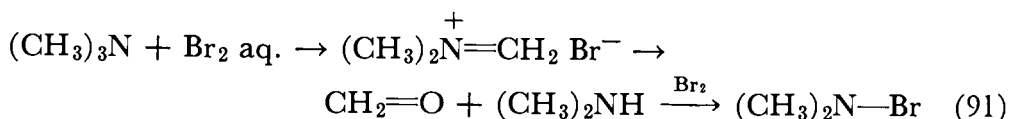
HALOGENATION N-Halogenation can be looked upon as a case of either oxidation or acylation (haloamines are amides of the hypohalous acids). Primary, secondary, and tertiary amines will react with all the common halogens, but since fluorine generally reacts with complete destruction of organic molecules, it will not be considered further. Chlorination has been the most studied, and will be the principal subject of this discussion.

N-Halogenation, unlike C-halogenation, is in general an ionic and not a free-radical process, and requires sources of "positive" halogen, such as the free elements, hypohalite salts, and tertiary alkyl hypohalites. Tertiary amines simply add halogen, to form N-halo quaternary halides ⁵⁸ (Eq. 90), analogous to the N-acyl quaternary halides formed with acid



halides. In the presence of water, however, elimination occurs, and the

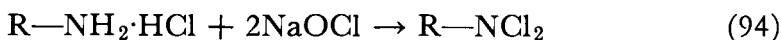
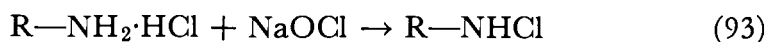
immonium compound thus formed becomes hydrolyzed to a carbonyl compound and a secondary amine (Eq. 91). Secondary amines react



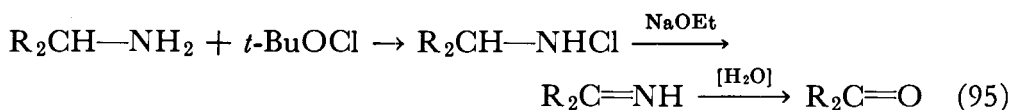
with either free halogen in aqueous solution buffered near neutrality (e.g., with sodium bicarbonate), or when their hydrochlorides are mixed with aqueous hypohalite solutions (Eq. 92). Reaction is generally quite



complete, and occurs readily in the cold. With primary amines, halogenation occurs in stages, and either N-chloro or N,N-dichloro compounds can be prepared by controlling the amount of hypochlorite ^{59a} or by use of *tert*-butyl hypochlorite ^{59b} (Eqs. 93, 94). When halogenation is com-

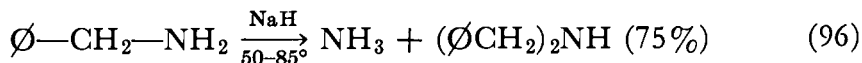


bined with base-catalyzed elimination, a useful oxidation to ketones or their imines results ^{59b} (Eq. 95).



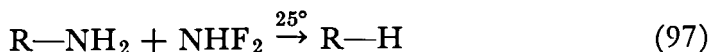
N-Haloamines are reactive substances, and may be converted to secondary products during attempted synthesis before they can be isolated; in some cases this amounts in the end to a form of oxidation as just noted. Such reactions will be discussed in the general context of the reactions of N-haloamines in Chapter 5.

DEALKYLATION AND DEAMINATION In addition to the oxidative dealkylation and nitrosative deamination reactions previously discussed, there are some other interesting reactions that can be classed as deaminations or dealkylations. Benzylamine is converted by sodium hydride to dibenzylamine and ammonia (Eq. 96); although the yield is good, the



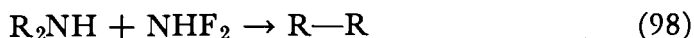
reaction does not appear to be general.⁶⁰ It is believed to take place through nucleophilic displacement by OCH_2-NH^- on the α -carbon of a second molecule. Difluoroamine replaces the amino group of primary amines by hydrogen, apparently through reaction of NF to form unstable

$R-N=N-H$ ^{61a} (Eq. 97). When secondary amines are treated with

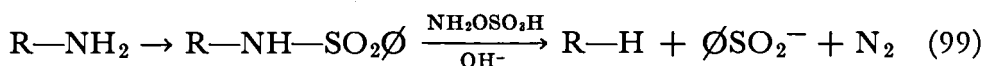


difluoroamine, bialkyls are formed (Eq. 98), presumably through inter-

mediate azamines, $R_2\overset{+}{N}=N^-$ (cf. oxidation of hydrazines, Chapter 9).



Replacement of an amino group by hydrogen can also be accomplished in a more roundabout way, in yields that are variable but often good, through reaction of the benzenesulfonyl derivative of an amine with hydroxylamine-O-sulfonic acid (Eq. 99); the same unstable intermediate

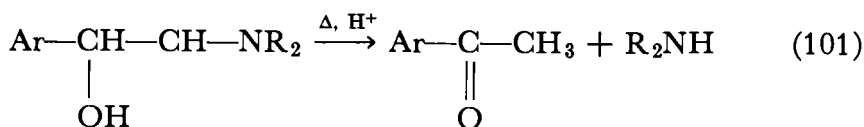


diazene is believed to be involved. ^{61b}

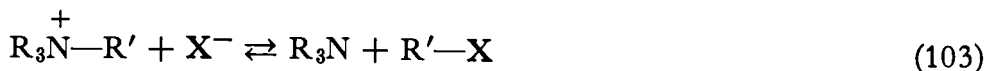
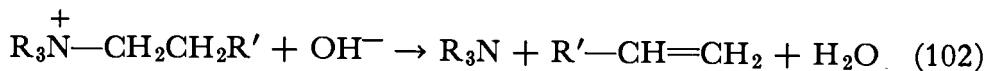
ELIMINATION Dealkylation by elimination of olefin is a practical procedure when a tertiary alkyl group is present. ^{62a} The change is effected by fusing the hydrochlorides or by refluxing in 6N hydrochloric acid, and the group preferentially eliminated is that one that would be expected to form the most stable carbonium ion (Eq. 100). All classes

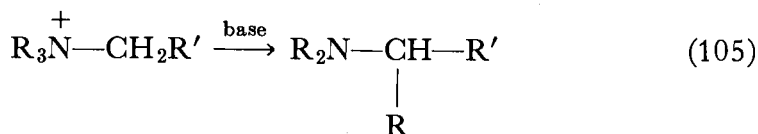


of amines are susceptible. This reaction is obviously closely related to the so-called "hydramine split," by which β -hydroxy amines are converted to aldehydes or ketones ^{62b,c} (Eq. 101).

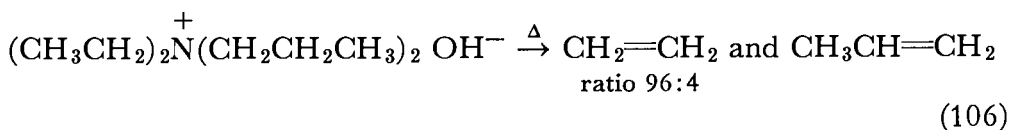


QUATERNARY COMPOUNDS The reactions of quaternary ammonium compounds will now be discussed; they are considered separately from the other classes of amines because their lack of an unshared electron pair markedly limits the scope of their reactivity. There are, in fact, only four significant reactions: elimination (Hofmann degradation); displacement; reductive cleavage; and rearrangement (Eqs. 102-105). They are ordinarily inert to oxidation.

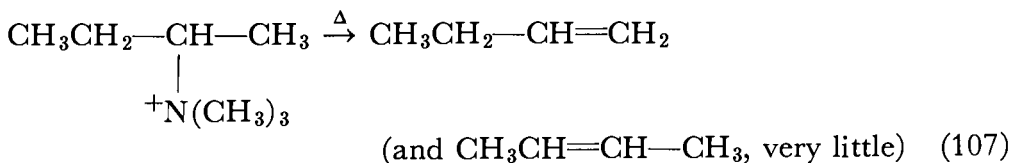




The Hofmann elimination is one of the oldest reactions of organic chemistry, having been reported in 1851. It is customarily accomplished by treating a solution of a quaternary ammonium halide with silver oxide to convert it to the hydroxide, and evaporating the resulting solution to dryness and heating strongly. Hofmann's original studies led him to make the generalization that when an ethyl group is attached to nitrogen, it is always eliminated, as ethylene, in preference to any other group. This rule has been gradually expanded over the years, and a more useful statement is that the alkyl group with the largest number of β -hydrogens is preferentially eliminated. Although this rule, which has come to be known as the Hofmann rule, is of great significance in the theory of elimination reactions, it is only approximate, and is only valid when complicating factors, such as the presence of other activating groups, or branching at the α -carbon, are absent. As examples of its operation, diethyldipropylammonium hydroxide gives 96% of ethylene ^{63a} (Eq. 106), and *sec*-butyltrimethylammonium hydroxide gives nearly all

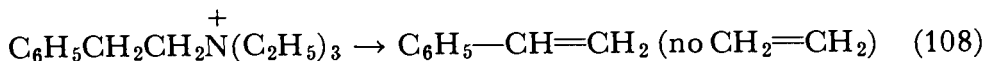


butene-1 and little butene-2 ^{63b} (Eq. 107).



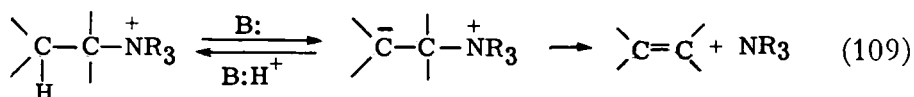
HOFMANN ELIMINATION The Hofmann elimination is of use in synthesis as a reliable way of introducing a terminal double bond, which is often difficult or impossible to achieve by dehydration of alcohols or dehydrohalogenation of alkyl halides. On the other hand, groups that activate a hydrogen, such as carbonyl, and even phenyl, cause Hofmann elimination to occur entirely in their direction if they are attached to a β -carbon; thus β -phenylethyltriethylammonium hydroxide gives only

styrene (Eq. 108). With strongly activating β -substituents, elimination

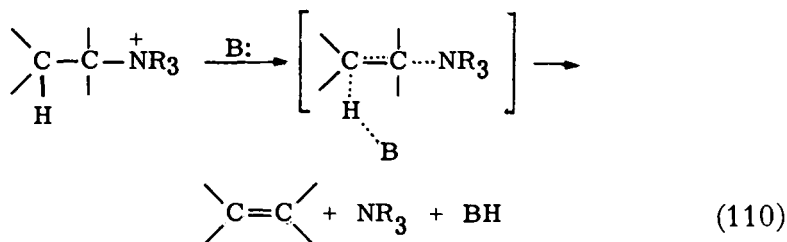


can occur so easily that heating may not be required.

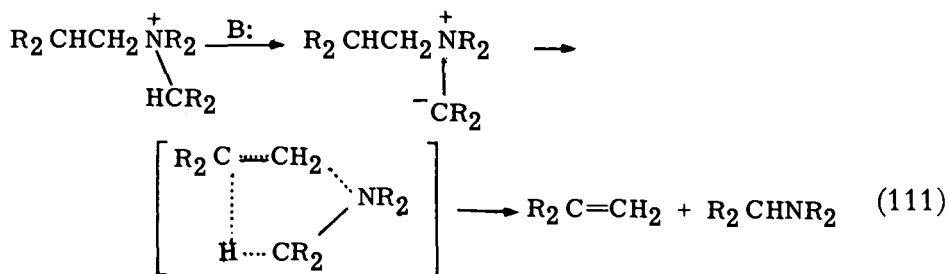
Studies of the mechanism of the Hofmann elimination⁶⁴ have been considerably inspired by the striking fact that the Hofmann rule is precisely the opposite of the Saytseff rule, which applies to the base-catalyzed formation of olefins from alkyl halides. To seek an understanding of the reason for this difference, one should first consider how the elimination might proceed; there are three reasonable possibilities. A nucleophile (hydroxide ion, solvent molecule, or other) may remove a proton from a β -carbon, giving an intermediate zwitterion, which can then either recombine with a proton, or simply cleave at the carbon-nitrogen bond to give an olefin and a tertiary amine (Eq. 109). The transition state for the



conversion of the quaternary ion to a zwitterion may be so close to that for cleavage that the two steps are effectively telescoped into one. In the limiting case, the zwitterion never has an independent existence, and it cannot equilibrate reversibly with the parent cation (Eq. 110). The third



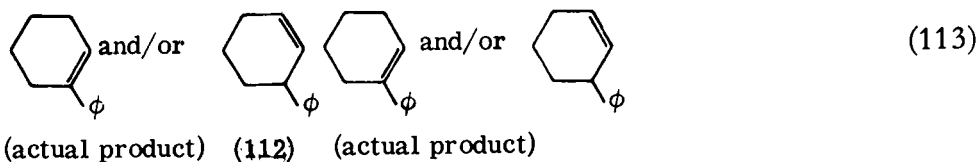
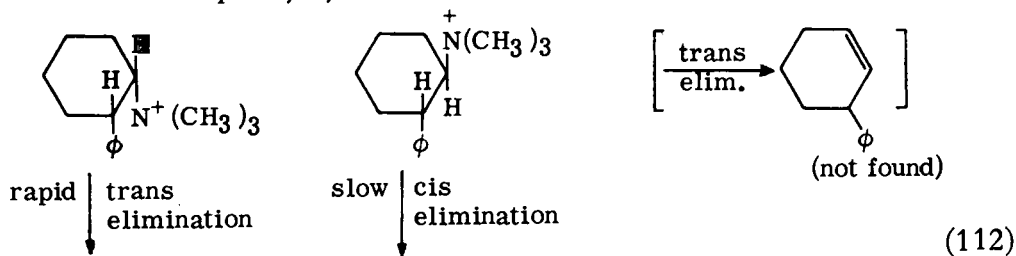
possibility^{64e} is the removal of a proton from an α -carbon, forming an ylide, which then decomposes through a cyclic transition state involving a β -hydrogen of one of the other groups (Eq. 111).



After the experiments that defined the structural scope of the Hofmann reaction came experiments with deuterium-labeled amines. These showed that there is no exchange of protons between the β -hydrogens and

water during the reaction, from which one may conclude that a reversible proton removal, $R-CH_2CH_2NR_3 + OH^- \rightleftharpoons H_2O + R-\overset{+}{C}HCH_2NR_3$, is not part of the reaction. It thus appears that the attack of hydroxide ion on a β -hydrogen is concerted with the cleavage of the carbon-nitrogen bond. The Hofmann rule might then reasonably be expected as a combined result of the statistical effect of a greater number of β -hydrogens, and differences in steric hindrance to attack. The stability of the ultimate olefin would be without influence if every properly oriented collision results in reaction. (In Saytseff-rule eliminations, on the other hand, the opposite situation occurs, and the stability of the resulting olefin dominates the elimination reactions of alkyl halides.) It should be clear, however, that this interpretation is strictly valid only for the quaternary amines with which the isotope experiments were conducted, and with great probability for amines of similar structure. It is not uncommon for mechanism to change according to structure, and there is reason to believe that a two-step elimination, involving reversible proton removal, operates in compounds with activated β -hydrogens.

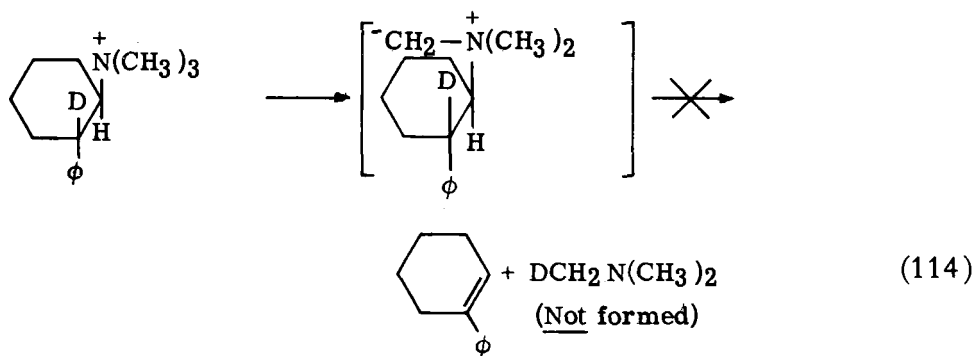
Attempts to distinguish between the concerted and the two-stage paths for the Hofmann elimination have been made by making use of the requirement that a concerted process have a nearly *trans* configuration in the transition state. The use of a cyclic system, where rotation is prevented, allows this point to be tested. 2-Phenylcyclohexylamine exists in a *cis* and a *trans* form, and separate quaternary ammonium hydroxides can be prepared from each. In the *trans* isomer, a fully concerted process must lead to 3-phenylcyclohexene, while in the *cis* isomer, either 1- or 3-phenylcyclohexene could be formed, for there is a hydrogen *trans* to the amino group on both the 2- and the 6-carbon atoms. The experiment showed that 1-phenylcyclohexene is formed in each case (Eqs. 112, 113)



but the reaction is much slower with the *cis* isomer.^{64f,g} After it was further established that neither the stereoisomeric starting materials nor

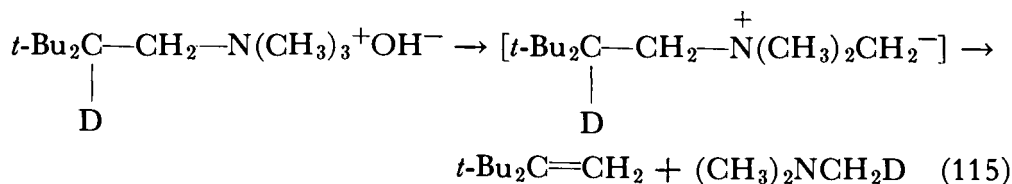
the isomeric phenylcyclohexenes were interconverted under the conditions of the reaction, it became necessary in the case of the *trans* isomer to accept the possibility of some sort of *cis* elimination that did not allow exchange of β -hydrogens with the environment through reversible proton removal. A two-step process in which the carbanion, once formed, decomposes to olefin and a tertiary amine at a hundred times (or more) the speed of its formation would meet the requirement.

An alternative path for *cis* elimination exists through initial removal of an α -hydrogen instead of a β , followed by internal proton transfer from a β -position. This path, known as the "ylide mechanism," has been disproved for the ordinary Hofmann reaction by experiments with deuterium-labeled amines ^{65a,b} (Eq. 114), although it may play a role in



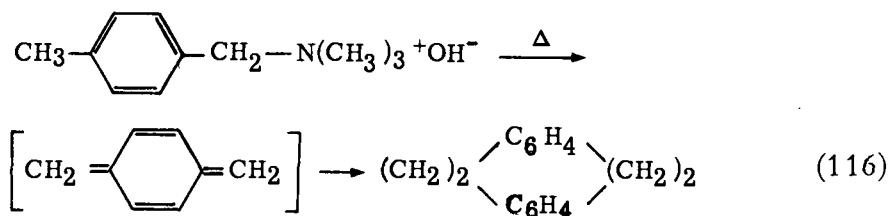
(disproof of the ylide mechanism)

eliminations brought about by treating quaternary ammonium salts with alkyl or aryllithium reagents.^{65c} The ylide pathway has been demonstrated in a special instance, however, where steric factors strongly favor a conformation suitable only for *cis* elimination ^{65d}; 2,2-di-*tert*-butylethyltrimethylammonium hydroxide bearing deuterium on the 2-carbon cleaves to di-*tert*-butylethylene and deuterated trimethylamine (Eq. 115).

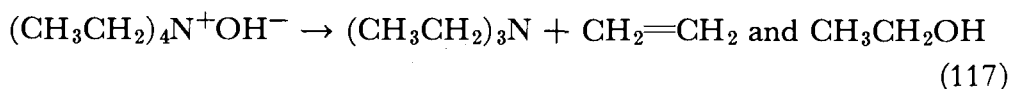


Further evidence for concerted elimination in the general case is found in kinetic isotope effects.^{65b, 66} Deuterium on the β -carbon retards the reaction, although the effect is less than in elimination with other types of compounds (e.g., alkyl halides). Substitution of N^{15} for N^{14} also retards elimination; for ethyltrimethylammonium hydroxide, $K_{\text{N}^{14}}/K_{\text{N}^{15}}$ is 1.017. These observations are interpreted to mean that severance of the C—N bond is concerted with removal of the β -hydrogen, and is characterized by appreciably advanced bond breaking in the transition state.

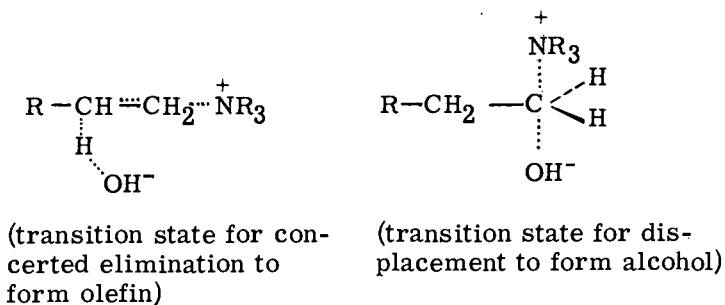
A benzologous 1,6-elimination has been observed with *p*-methylbenzyltrimethylammonium hydroxide, which yields [2.2]paracyclophane ¹⁷ (Eq. 116).



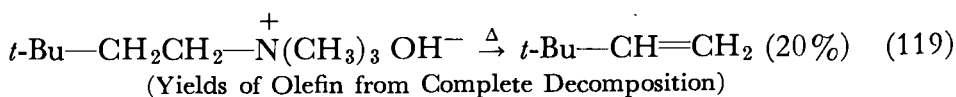
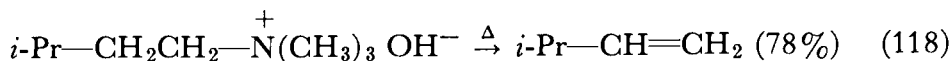
DISPLACEMENT The Hofmann elimination cannot be fully discussed without at the same time considering the displacement reaction, which is an ever-present competitor. The decomposition of quaternary ammonium hydroxide may give not only olefin, but also alcohol (Eq. 117).



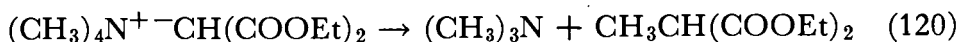
The amount of alcohol formed is usually small, often negligible, unless steric factors are present that retard elimination. There is no question of alcohol formation being other than a competing process, because under the alkaline conditions of the reaction, olefins are not in the least hydrated to alcohols. There must, therefore, be a displacement by hydroxide ion on an α -carbon. It is consistent with this that the groups



most readily removed as alcohols, such as methyl and benzyl, are those that in general provide the most favorable sites for nucleophilic displacement when they are attached to other types of displaceable functions. When Hofmann elimination is retarded by bulky substitution about the β -carbons, displacement may become the major reaction (Eqs. 118, 119).

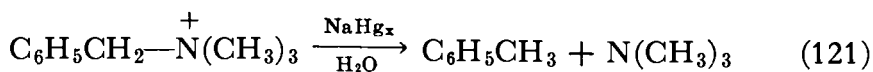


Like all displacement reactions, this one is promoted by strong nucleophiles, while the elimination reaction is promoted by strong base. It is therefore possible to control somewhat the relative extents of elimination and displacement by careful choice of reagent. Carbanions, being particularly strong nucleophiles, are successful displacing agents; the result is C-alkylation, a reaction of much synthetic application ⁶⁸ (Eq. 120).



Displacement can also be accomplished by halides, thiocyanate, ^{69a} carboxylate, ^{69b} or hydrosulfide ^{69c} ions, and by amines, particularly ethanolamine, ^{69d} when quaternary salts are heated strongly. The general rule is that the smallest alkyl group comes off most readily, although exceptions have been noted. The generalization is consistent with both possibilities, that the smallest alkyl group is displaced fastest owing to having the least steric hindrance, and that multicomponent equilibrium between quaternary salts, amines, and alkyl halides would be shifted in the direction that produces the most volatile product. This is the basis of the Herzig-Meyer N-methyl determination, in which N-methyl groups are estimated by determining the amount of methyl iodide produced by heating the amine with hydriodic acid. It is successful with amines of all classes, for constant-boiling hydriodic acid is much less volatile than methyl iodide. The latter is conveniently determined by reaction with silver nitrate. N-Phenyl groups retard elimination in favor of displacement of an alkyl group. ⁷⁰

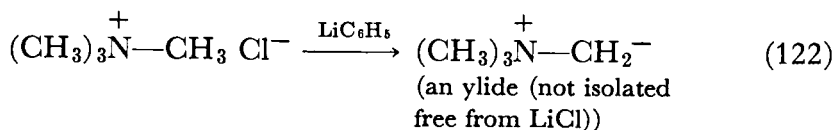
REDUCTION Emde reduction is a somewhat uncommon reaction, in which a group is removed reductively from a quaternary nitrogen. ⁷¹ Sodium in various forms, electrolysis, and the zinc-copper couple have been used. The selectivity of the reaction is quite different from dealkylation by Hofmann elimination or by displacement; the removed group is generally the one that would form the most stable free radical (Eq. 121).



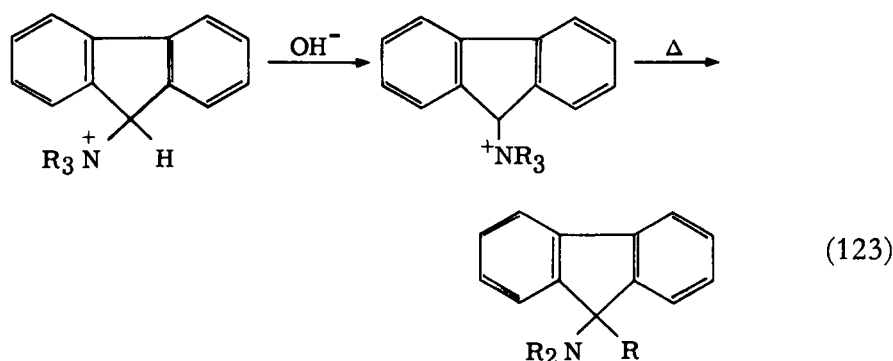
Initial reduction to an ammonium radical, which then cleaves into a tertiary amine and an alkyl or aryl radical, accounts for most of the facts, although there is reason to believe that carbanions are also intermediates in some cases. Lithium aluminum hydride also cleaves quaternary ammonium ions reductively ^{71c}; the yields of tertiary amine are good, and a methyl is removed preferentially to other groups.

YLIDES Bases can attack not only β -hydrogens and α -carbons, but also α -hydrogens. The immediate result is a zwitterion, in which a semi-

polar double bond can be considered to have been formed between carbon and nitrogen (Eq. 122). Such compounds have been termed

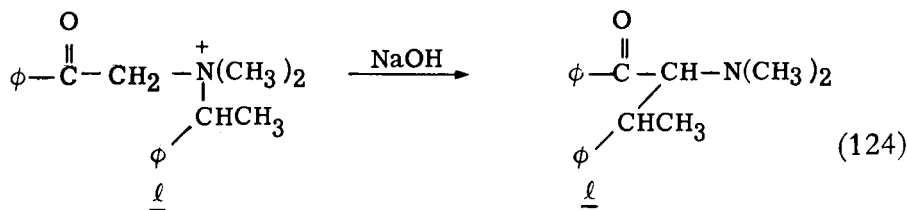


“ylides” by Wittig,⁷² who has done the most to reveal their characteristics. Many examples have actually been isolated. They react much as other carbanions, hydrolyzing readily to regenerate the quaternary ion, and adding to carbonyl groups. They also undergo rearrangement (Eq. 123),



especially when heated, in such a way as to get rid of the separation of charge. A group migrates intramolecularly from nitrogen to carbon, giving a tertiary amine isomeric with the ylide.

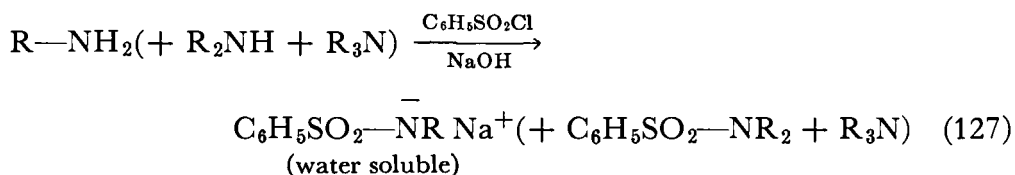
STEVENS REARRANGEMENT This rearrangement is known as the Stevens rearrangement,⁷³ and was known long before the intermediacy of ylides was demonstrated. It is effectively a base-catalyzed reaction of quaternary amines, and can be expected whenever a quaternary amine with an especially activated α -hydrogen is treated with strong bases, such as sodium amide or alkoxides (Eq. 124). The migrating carbon retains its



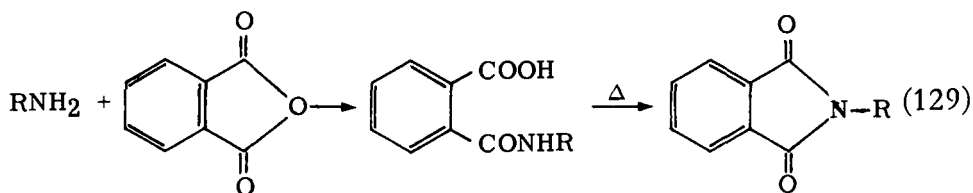
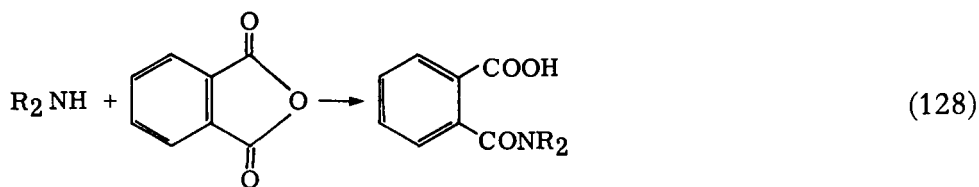
optical configuration, and the reaction is intramolecular.

SOMMELET REARRANGEMENT Another rearrangement, known as the Sommelet,^{73, 74} may compete with the Stevens when benzyl groups are attached to quaternary nitrogen. A benzyl group migrates to the anionic

When amines are prepared in this way, the problem of separation of primary, secondary, and tertiary amines comes up. There is really no difficulty when the alkyl group is big (butyl, for example), for there are then large differences in both boiling point and solubility of the several products. Only with small alkyl groups, particularly methyl, are special methods called for. The classical method is the Hinsberg separation, in which the mixture is treated with excess benzenesulfonyl chloride. Primary amines form benzenesulfonamides that contain an acidic N—H, and are thus generally soluble in aqueous base; secondary amines form sulfonamides that are neutral, since they have no N—H, and tertiary amines do not react, remaining basic. By treating the mixed acylation products with aqueous base, the benzenesulfonated primary amine can usually be dissolved out (Eq. 127) (some exceptions occur, and sometimes

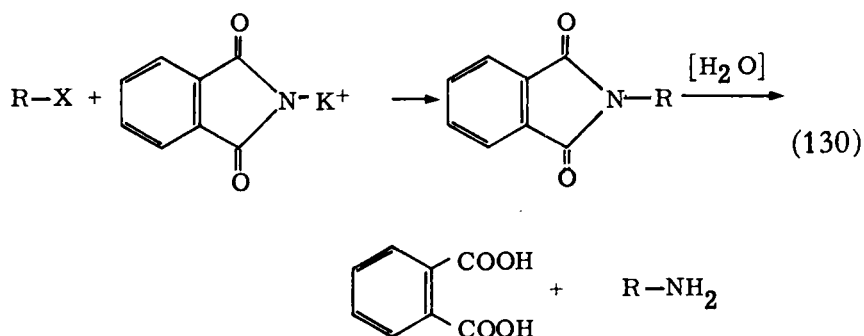


a neutral, diacyl derivative is formed). Although the free primary amine can in principle be regenerated by hydrolyzing the purified sulfonamide, the process is often tedious and is rarely of synthetic value. The Hinsberg separation is of much greater value as an analytical method. An alternative method uses phthalic anhydrides⁷⁶; primary and secondary amines form phthalamic acids. Heating the phthalamic acids derived from primary amines converts them to N-alkyl phthalimides, which, being neutral, are easily separated from the unaltered N,N-dialkylphthalamic acids (Eqs. 128, 129).



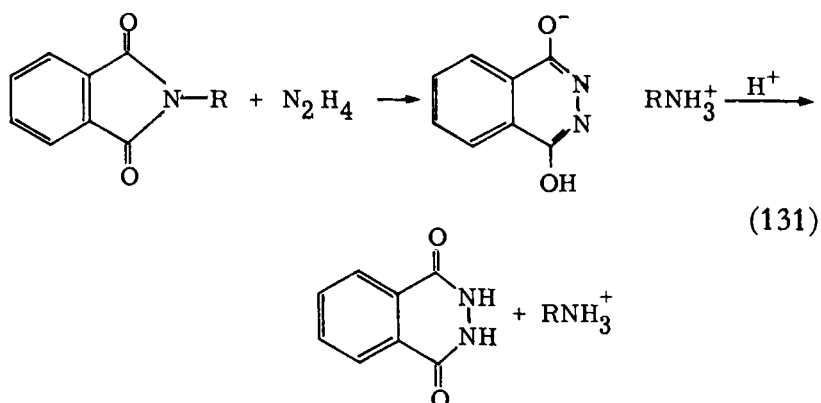
One group of preparative methods for primary amines is based on the principle of blocking the hydrogens of ammonia in such a way that only monoalkylation is possible. The most important of these is the Gabriel phthalimide synthesis (Chapter 4), in which the bidentate

phthaloyl group blocks two of the positions on ammonia (Eq. 130).



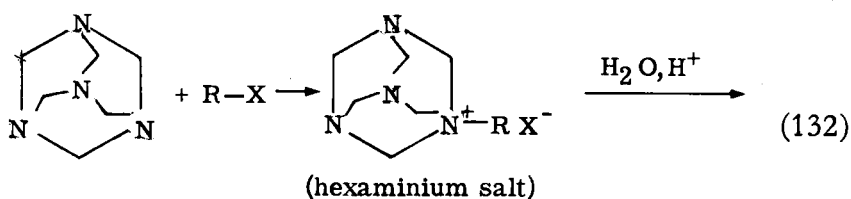
Phthalimide itself is not sufficiently nucleophilic to react with alkylating agents, and it must be converted to its anion for use. Even so, the phthalimide anion is not a powerful nucleophile, and alkylation of it is often slow. The use of dimethylformamide as a mutual solvent for potassium phthalimide and alkylating agents accelerates the reaction so much that it may even become spontaneous and exothermic, and gives excellent yields.⁷⁷ Hydrolysis of the N-alkyl phthalimide produced then yields a primary amine uncontaminated with secondary or tertiary amine. The process is obviously limited to those alkyl groups that undergo displacement reactions readily, so that tertiary alkyl groups, along with many groups having cycloalkyl or isobutyl structures, cannot be prepared by the Gabriel synthesis.

Hydrolysis of phthalimides is generally very tedious, whether catalyzed by acid or base, necessitating the use of sealed bomb tubes for completion. This causes extra trouble, and limits the reaction to small batches, and thus constitutes a major bottleneck in the use of the Gabriel method. The practicality of the synthesis was enormously improved with the discovery of a simple, fast cleavage method. Ing and Manske found that hydrazine reacts readily with phthalimides when the two are warmed briefly on the steam bath, and treatment of the reaction mixture with hydrochloric acid at once precipitated insoluble phthalhydrazide and gave a solution of the amine hydrochloride (Eq. 131). The intermediate

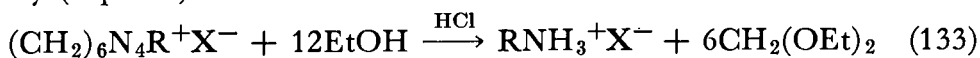


compound is the amine salt of phthalhydrazide, which is a weak acid. The salt can therefore be broken up not only by strong acids, but also by alkalies, and even by heat alone.

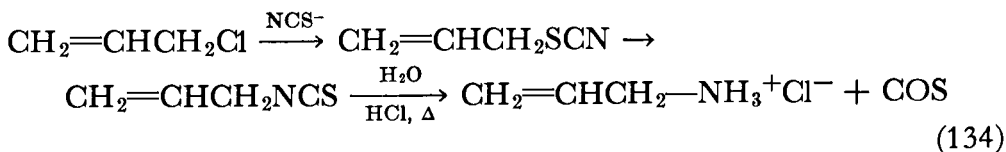
The Delépine synthesis ⁵⁶ of primary amines makes use of methylene groups rather than carbonyl groups to block more than monoalkylation of nitrogen; the trick, of course, is to use methylene groups that can be easily removed after the desired alkylation. Hexamethylenetetramine ("hexamine") fulfills the requirements; it is a tertiary amine, but it is hydrolyzed to (as well as formed from) formaldehyde and ammonia. Although it has four equivalent nitrogens, it is only a weak base and a weak nucleophile, and accepts only one alkyl group from alkylating agents, giving rise to "hexaminium" salts. Hydrolysis then gives formaldehyde, ammonia, and the desired primary amine (Eq. 132).



Because of the poor nucleophilic properties of hexamine, only particularly reactive alkylating agents can be used, and for synthetic purposes the group is limited largely to primary benzylic and allylic halides. Iodides are of course more effective, but sodium iodide is a helpful catalyst when chlorides or bromides must be used; refluxing the reagents in alcohol for a few hours or several days is usually required. The subsequent hydrolysis step must be conducted with care to avoid the incursion of the Sommelet reaction, which would convert the alkyl group to an aldehyde (see p. 50). The most reliable process seems to be the use of alcoholysis, accomplished by passing dry hydrogen chloride into the reaction mixture. This converts the methylene groups to diethyl formal, which is distilled away (Eq. 133).

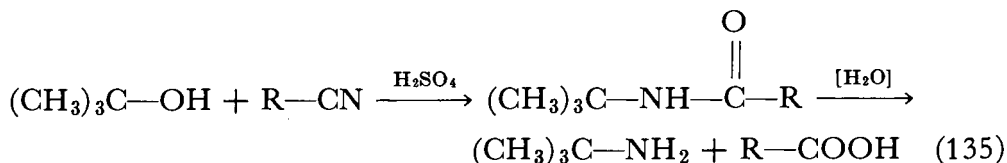


A third way to block alkylation of ammonia is to involve three of its bonds in a triple bond, i.e., to use nitriles. Both thiocyanate ion, $\text{N}\equiv\text{C}-\text{S}^-$, and alkyl cyanides have been used for this purpose. Alkylation of thiocyanate salts goes for the most part on sulfur, producing alkyl thiocyanates, $\text{R}-\text{S}-\text{C}\equiv\text{N}$, which must be rearranged to isothiocyanates, $\text{R}-\text{N}=\text{C}=\text{S}$, before an amine can be obtained by hydrolysis ⁷⁶ (Eq. 134)

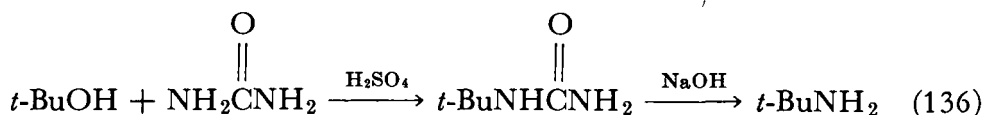


(see Chapter 6). As this is usually difficult and inefficient except with allylic groups, the synthetic utilization is severely limited.

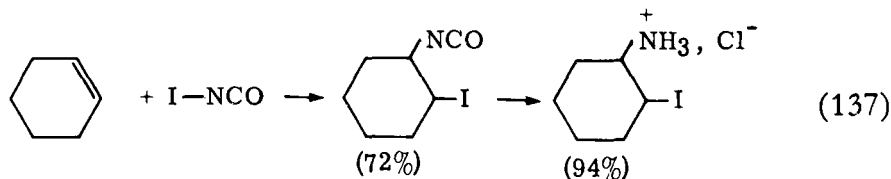
Alkylation of nitriles cannot be accomplished by ordinary means, for the nitrogen of nitriles is an extremely poor nucleophile. Under strongly acidic conditions, where carbonium ions can be expected, tertiary alcohols and the corresponding olefins react with nitriles to form N-alkyl amides, which are easily hydrolyzed to primary amines ^{79a} (Ritter reaction, Eq. 135; see Chapter 5). Hydrogen cyanide is conveniently used in this



reaction, a suspension of sodium cyanide in glacial acetic acid being suitable. This synthesis of primary amines is a valuable complement to the other alkylation processes, for it gives amines with tertiary alkyl groups, not accessible by the other methods. This same feature applies to the synthesis of amines by acid-catalyzed alkylation of urea with tertiary alcohols, followed by hydrolysis ^{79b} (Eq. 136).



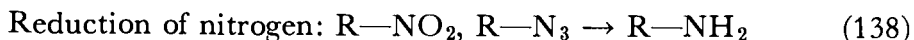
β -Haloamines can be prepared by addition of various N—X compounds, such as chlorourea, to olefins. Of particular success is the use of iodine cyanate, which can be prepared from silver cyanate and iodine and used without isolation (Eq. 137); the β -iodo isocyanates formed are



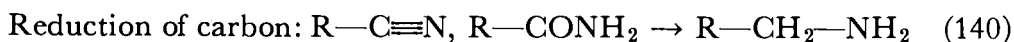
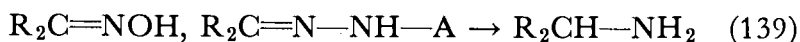
easily hydrolyzed.⁸⁰

In principle, any organic nitrogen compound can be reduced to the oxidation stage of an amine, and when in the original compound the nitrogen is bound only to one carbon, the result is a primary amine. Of the many possible types of starting materials for reductive synthesis of primary amines, only a limited number have significant synthetic application: nitro compounds, azides, oximes, hydrazones, imines, amides, and nitriles. In the first two classes, nitrogen is being reduced; in the second

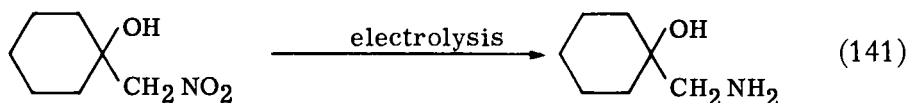
two, nitrogen and carbon, and in the last three, only carbon (Eqs. 138–140).



Reduction of nitrogen and carbon:

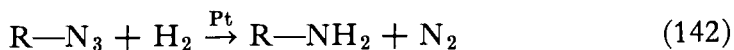


The reduction of nitro compounds is not so important a method of synthesis of aliphatic amines as of aromatic, owing to the more limited accessibility of aliphatic nitro compounds. Alkyl halides and thus alcohols or olefins are convertible to simple nitro compounds in good yield by general reactions,⁸¹ but direct nitration of any but the simplest aliphatic hydrocarbons produces complex mixtures. The most useful sources of aliphatic nitro compounds for the synthesis of amines are the condensation reactions of the small commercially available compounds, nitromethane, nitroethane, and the nitropropanes. Reduction has been accomplished by hydrogenation, by electrolysis (Eq. 141), by various metals, such as



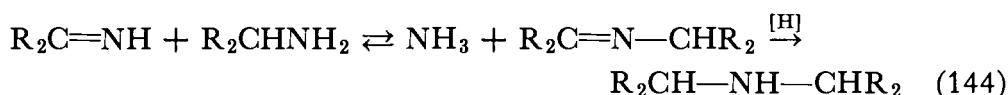
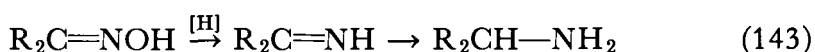
iron, zinc, and tin, in the presence of strong acids, and in contrast to aromatic nitro compounds, with lithium aluminum hydride.

Reduction of alkyl azides⁸² is a synthesis for primary amines of potentially wide scope, for primary and secondary alkyl azides can be prepared from olefins and alcohols through the reaction of alkyl halides or toluene-sulfonates with sodium azide (see Chapter 10). Reduction succeeds by catalytic hydrogenation (Eq. 142), by tin or stannous chloride, or by



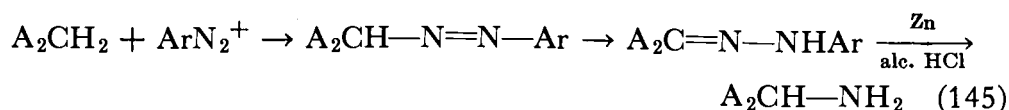
lithium aluminum hydride or sodium borohydride. It is a peculiarity of hydrogenation that there is no net change of gas volume, the uptake of hydrogen being balanced by evolution of nitrogen, and the course of the reaction cannot be followed by volumetric means. Lithium aluminum hydride reacts fast, and, of course, reduces many other functional groups that may be present; sodium borohydride is far more selective, but reacts much more slowly, and must be used in excess in isopropyl alcohol for success.

The reduction of oximes (Chapter 8) is an old and widely used synthesis⁸⁸ of primary amines and is possible starting with almost any ketone or aldehyde. In addition, many oximes are available by direct nitrosation of active methylene groups. The most widely used methods are catalytic hydrogenation and treatment with excess metallic sodium in hot alcohol, although tin, zinc, aluminum amalgam, lithium aluminum hydride, and electrolysis have been used. It is not usually satisfactory to use the metal-plus-acid combinations, owing to the fact that oximes are hydrolyzed by hot acid. Catalytic hydrogenation often produces significant quantities of secondary amine. The only reasonable path for the formation of such products is the reduction of an N-alkyl imine, which could in principle arise from the reaction of some primary amine with either unchanged oxime or with an intermediate imine (Eqs. 143, 144). Since oximes are

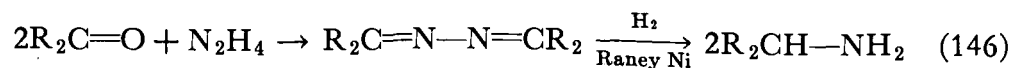


ordinarily inert toward amines, it is presumably the imines that are involved. This undesirable side reaction can be minimized in two ways, both of which act through the equilibrium apparently operating at the intermediate stage. In one way, the reduction is carried out in the presence of excess ammonia, which greatly reduces the equilibrium concentration of N-alkyl imine, $R_2C=N-CHR_2$; in the other, the reduction is carried out in the presence of acetic anhydride, which reacts with the primary amine faster than it can equilibrate with the intermediate imine.

The reduction of hydrazones (Chapter 9) is similar to reduction of oximes, but is not as widely used. Unsubstituted hydrazones are not generally convenient to prepare, but semicarbazones and arylhydrazones usually serve as well. In addition to their synthesis from aldehydes and ketones, some can be prepared by the coupling of diazonium salts with active methylene groups (Japp-Klingemann reaction, see Chapter 11) (Eq. 145). Azines, $R_2C=N-N=CR_2$, the double hydrazones derived



from hydrazine, have also been used (Eq. 146). Both hydrogenation



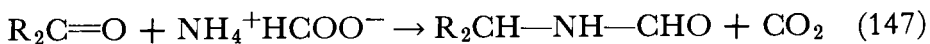
over Raney nickel, and zinc dust with alcoholic hydrogen chloride, have been used successfully.

Reduction of aldimines and ketimines¹⁶ is a simple addition of two atoms of hydrogen, and takes place readily with the usual hydrogenation catalysts, such as Raney nickel. The greatest use of this reaction as a synthesis for primary amines is in the reductive alkylation^{16, 84} of ammonia, in which imines are formed as intermediates but not isolated. It is also possible to prepare ketimines by the reaction of Grignard reagents with nitriles, and then hydrogenate them. Since imines are very easily hydrolyzed, they are not usually reduced by other means (cf. Chapter 7).

Although nitriles and amides represent the same oxidation state of carbon and nitrogen, there is a marked difference in their ease of reduction. Nitriles can be hydrogenated⁸⁵ catalytically easily at moderate pressures and at room temperature; the primary amine produced is likely to be contaminated with secondary amine for the same reason as in the reduction of oximes—equilibration of an intermediate imine with primary amine, and subsequent reduction of the N-alkyl imine. It can be avoided in the same ways. Nitriles are also reduced to amines by excess sodium in hot alcohol, a reaction that is seldom accompanied by secondary amine formation, probably because the reduction is so rapid that there is no time for equilibration at the imine stage. Lithium aluminum hydride is also a satisfactory, but more expensive reducing agent for nitriles (cf. Chapter 5).

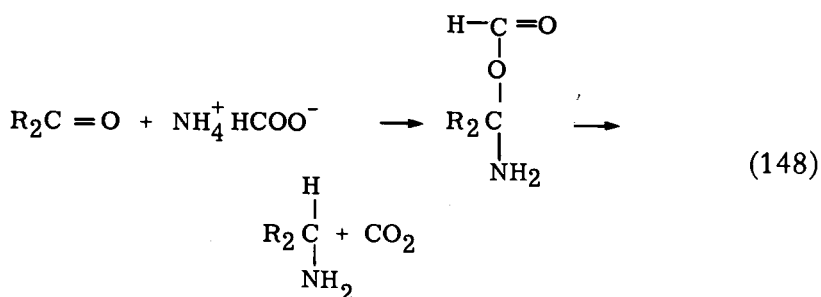
Amides are more resistant to reduction, and hydrogenation usually requires high pressures and heat; copper chromite has been a commonly used catalyst. Although sodium and alcohol will reduce some amides, it is not usually satisfactory; lithium aluminum hydride appears to be by far the best reducing agent for amides.

The Leuckart reaction⁸⁶ is clearly related to the reductive methods, particularly reductive alkylation of ammonia. As usually carried out, a ketone is heated with excess ammonium formate at about 160–170° for several hours; the formyl derivative of the amine is produced, commonly in yields of 50 to 80% (Eq. 147). Hydrolysis is, of course, easy

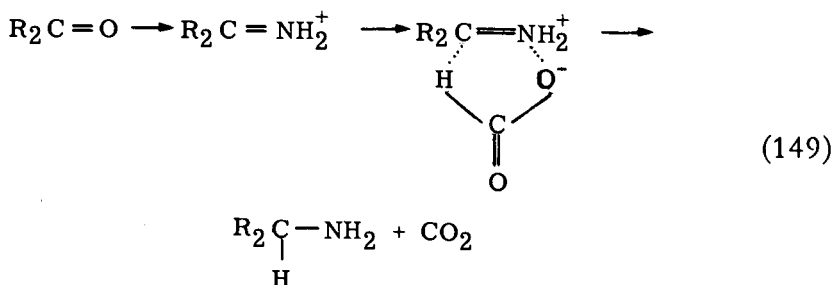


and quantitative. A distinct advantage is that other reducible groups, such as nitro, are not usually affected (but α,β -unsaturated ketones give resinous products). Aldehydes are not generally satisfactory in the Leuckart reaction, being liable to produce undesirably large amounts of secondary and tertiary amines. The deliberate application of the Leuckart reaction to the synthesis of secondary and tertiary amines will be taken up further on.

The mechanism of the Leuckart reaction has been the subject of much discussion. A point of uncertainty has been whether ammonium formate or formamide is the active agent; under the conditions of the reaction, ammonium formate equilibrates both with formamide and with ammonia and formic acid. Although the use of preformed formamide sometimes also produces amines, better yields seem to be obtained with ammonium formate. A claim has been made that the reaction of formamide is catalyzed by Lewis acids, such as heavy metal halides, but since the successful "catalysts" in every case contained water of hydration, it is equally possible that the results were due to the hydrolysis of formamide to ammonium formate. Additional insight into the nature of the reaction is given by the stereochemical results from ketones with asymmetric centers. 2-Methylcyclohexanone gives 2-methylcyclohexylamine that is 60% *cis* in configuration; for comparison, catalytic hydrogenation of the corresponding oxime gives 85% *cis* amine, whereas reduction of the oxime with sodium and alcohol gives 80% *trans* amine, the more stable isomer. Two reasonable proposals have been made ^{86b}: in one (Eq. 148),



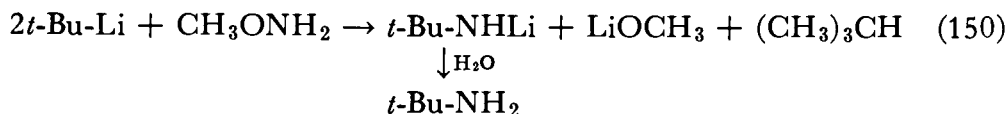
the formate ester of a carbinolamine is formed by obvious steps, and decomposes intramolecularly, in the manner known for simpler formate esters; in the other (Eq. 149), a ketimmonium ion is reduced by formate



ion through a cyclic transition complex. Both paths would be expected to result in some stereospecificity.

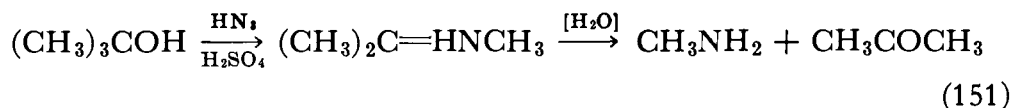
The preparation of primary amines from organolithium compounds of Grignard reagents is possible with four kinds of reagents: alkoxyamines,

chloramine, quaternary hydrazones, and sulfonyl azides, but only the reactions of the first two,⁸⁷ sometimes referred as the Kocheshkov synthesis, are of preparative value for aliphatic amines. Two moles of organometallic compound are consumed, one of which is lost as hydrocarbon (through reaction with the active hydrogens of the amino group) (Eq. 150). Since chloramine is objectionable to handle, and methoxy-

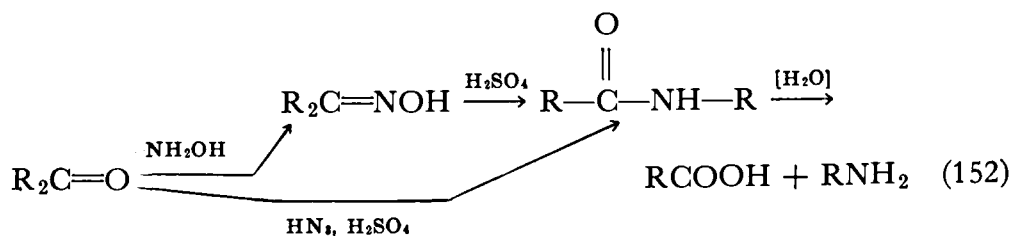


amine is tedious to prepare in the anhydrous state, benzyloxyamine has been recommended as the preferred reagent.

The last important class of syntheses of primary amines is the rearrangement reactions,⁸⁸ which can be subdivided into rearrangements of alcohol derivatives, of ketone derivatives, and of carboxyl derivatives. Alkyl azides are produced, rearranged, and the products hydrolyzed to amines by treatment of alcohols or olefins with hydrogen azide and strong acid (Eq. 151). This process is one of the varieties of the Schmidt



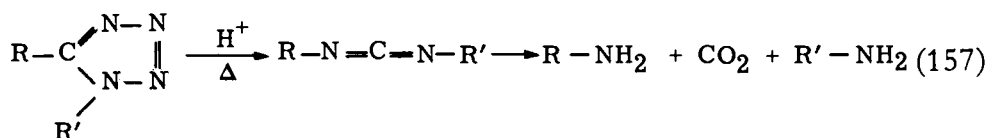
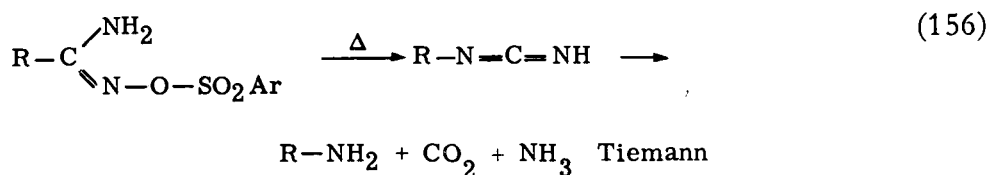
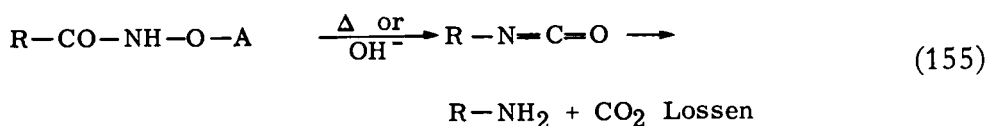
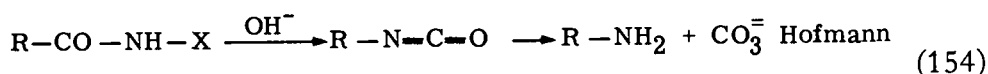
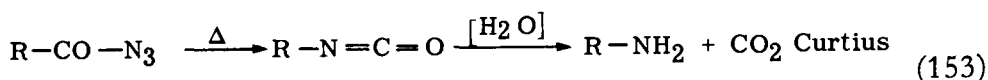
reaction, and although it sometimes works quite well, has not yet assumed importance as a synthetic method (see Chapter 10). The Beckmann rearrangement of oximes, which gives amides (see Chapter 8), is the best known of the ketone rearrangements, but the Schmidt reaction, between ketones and hydrogen azide, is also important (Eq. 152).



(Beckmann Rearrangement and Schmidt Reaction as Syntheses for Primary Amines)

The carboxyl derivatives that undergo rearrangement with eventual production of primary amines are the azides (Curtius rearrangement), N-haloamides (Hofmann rearrangement), hydroxamic acids (Lossen

rearrangement), amidoximes (Tiemann rearrangement), and 5-substituted tetrazoles (see Chapter 6) (Eqs. 153–157).



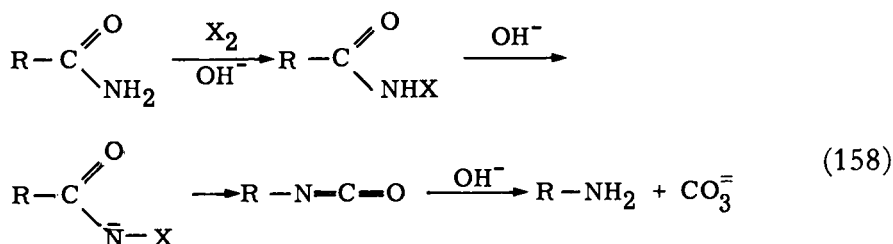
(Rearrangement of carboxyl derivatives leading to primary amines)

The Beckmann rearrangement, although a reaction of great importance,⁸⁹ has seen only little use as a synthesis of aliphatic primary amines. The reason is that unsymmetrical ketones give mixtures of amines resulting from both possible directions of rearrangement, and symmetrical ketones must usually be used to obtain a uniform product. Most syntheses of the required ketones add sufficient tediousness to the over-all process that alternative amine syntheses are almost always more efficient (this is no longer true with aromatic ketones; see Chapters 3 and 8).

The Schmidt reaction between ketones and hydrogen azide is a faster conversion of a ketone to an amide than is oximation followed by Beckmann rearrangement, but it still offers no distinct advantages over other methods for the synthesis of primary aliphatic amines.

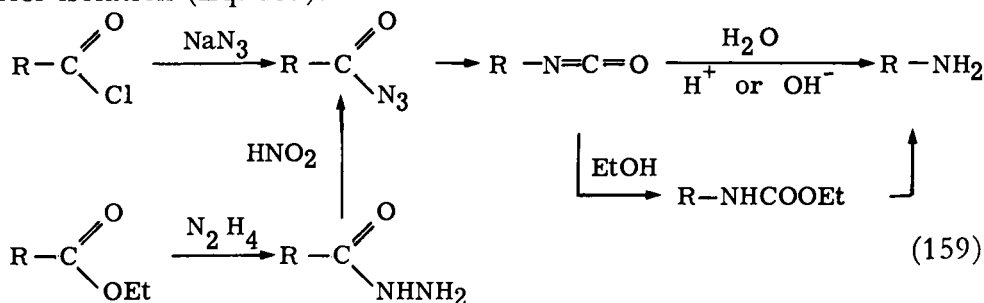
The rearrangement reactions of carboxyl derivatives have long been

important synthetic tools of the organic chemist. Although they all produce something other than a primary amine as the primary product, it is nearly always possible to proceed to the stage of a primary amine without isolation of intermediates, and usually without even changing reaction vessels. The Hofmann rearrangement⁹⁰ illustrates this clearly. As a laboratory procedure, an amide is treated with chlorine or bromine in the presence of aqueous alkali, and after brief warming, a primary amine of one less carbon atom usually separates. From a mechanistic standpoint, the process consists of several distinct stages, each of which can be arrested if proper care is taken. N-Haloamides are the first products, followed by their sodium or potassium salts, then isocyanates, then carbamate salts, and finally amine (Eq. 158). Only the amide has



to be made in a separate step.

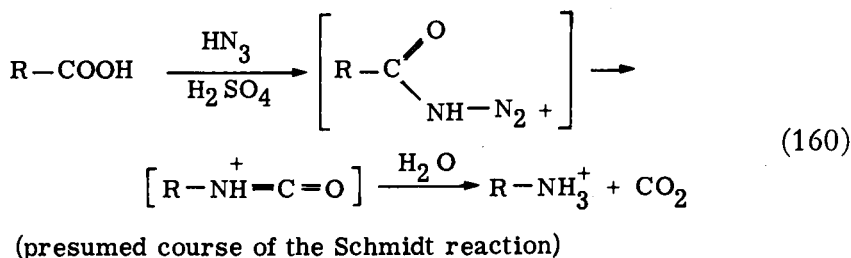
In the Curtius rearrangement,⁹¹ an acyl azide must first be made, almost invariably either by reaction of acyl chloride with sodium azide, or by treatment of a hydrazide with nitrous acid. The azides are not usually isolated, but are caused to rearrange by warming in solution. If the solvent is inert, an isocyanate is produced, and must be hydrolyzed; hot aqueous acid or base is effective, and isolation of the isocyanate is not required. If the solvent is an alcohol, the isocyanate is at once converted to a urethan, which must likewise be hydrolyzed, with or without prior isolation (Eq. 159).



(various pathways in the Curtius degradation)

In the closely related Schmidt reaction,⁹² a carboxylic acid is treated with hydrogen azide and concentrated sulfuric acid. The amine of one less carbon atom is formed directly (as its sulfate salt, of course), and carbon dioxide is evolved. Although no intermediates have been isolated, there is good reason to believe that the carboxyl group is first con-

verted to the conjugate acid of an acyl azide, which undergoes rapid rearrangement and hydrolysis (Eq. 160). The over-all process thus



differs from the Curtius rearrangement principally in passing through protonated intermediates. As would be expected in consequence of this, acyl azides previously prepared are converted quickly (even violently) to primary amines by contact with concentrated sulfuric acid. The simplicity and rapidity of the process are attractive, and the inconvenience of preparing and handling solutions of hydrogen azide can be avoided by adding solid sodium azide to the sulfuric-carboxylic acid mixture. On the debit side, concentrated sulfuric acid is a powerful reagent, which attacks many other organic structures and catalyzes various reactions. For this reason, ketone, alcohol, and olefin functions, among others, cannot be present without suffering alteration.

The Lossen rearrangement of hydroxamic acids⁹³ has seen much less synthetic application than the foregoing carboxyl derivative rearrangements, and it appears to offer no advantages. A hydroxamic acid must first be prepared, usually by reaction of an ester with hydroxylamine in the presence of strong base, and must then be acylated. Rearrangement and hydrolysis can be carried out without isolation of intermediates by warming the O-acyl hydroxamic acid with alkali.

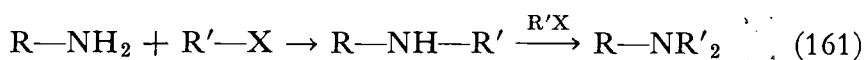
The Tiemann rearrangement and the degradation of tetrazoles have as yet seen no effective use as synthetic methods for primary amines.

The mechanisms of the various rearrangements of carboxyl derivatives to isocyanates or related structures are closely related. They have in common the migration of a group from carbon to nitrogen accompanied by the departure from the nitrogen of either a stable molecule (e.g., N₂) or a stable anion (e.g., Cl⁻). It is not clearly settled whether these two processes are concerted or whether the latter occurs as a discrete initial step, producing an acyl azene, R—CO—N̈:, as a fleeting common intermediate. It would not be unreasonable to suppose that there actually exists a continuous spectrum from one extreme to the other, with the behavior depending on structure and experimental conditions. The migration step is in any event intramolecular, and has been shown to occur with retention of configuration when the migrating carbon is a seat

of optical asymmetry. Fuller details of the mechanisms of all these rearrangements can be found elsewhere ⁸⁸ (see also Chapters 4, 8, and 10).

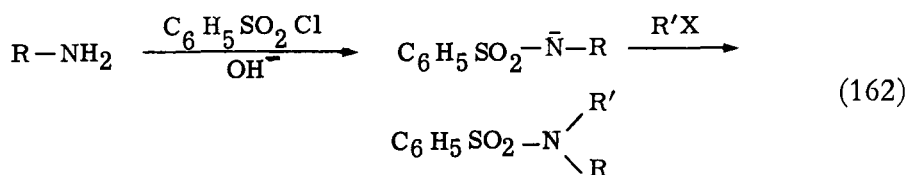
B. Secondary Amines

Syntheses of secondary amines are somewhat more limited in variety than those of primary amines. Alkylation of primary amines is perhaps the commonest method, and certainly the oldest. It is subject to all the limitations that have been mentioned earlier in this chapter for alkylation reactions, and they need not be repeated here. The problem of controlling the alkylation so as to stop at the secondary amine stage (Eq. 161) is of great importance.¹²



Steric effects act to inhibit polyalkylation, and with alkylating agents of moderate bulk, the danger of the reaction proceeding to a tertiary amine is small.^{12f} Often, however, the chemist wishes to methylate a primary amine, or to add some similarly small group. It is, of course, possible to minimize tertiary amine formation by using a large excess of primary amine, but this is not of synthetic value when one wants to alkylate a valuable amine with a common alkylating agent, the usual circumstances. The other alternative is to block one of the positions on the primary amine, in analogy to methods used in the alkylation of ammonia to primary amines.

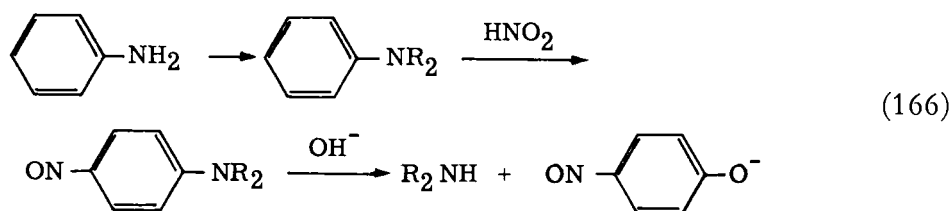
Five blocking groups are of practical value: sulfonyl, cyano, benzyldene, α -alkoxyalkylidene, and phenyl. To use the first of these, a primary amine is treated with benzenesulfonyl chloride in the presence of aqueous alkali, and the resulting solution of the sodium salt of an N-alkylbenzenesulfonamide is treated directly with alkylating agent; the benzenesulfonyl derivative of the secondary amine usually separates rapidly (Eq. 162). Removal of the benzenesulfonyl group by hydrolysis may be



tedious and require drastic conditions, but is generally successful. Reduction to more easily hydrolyzed sulfinic acid derivatives offers advantage in this step; metallic zinc, or hydrogen bromide plus phenol, have been used successfully (see Chapter 4).

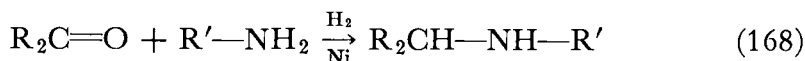
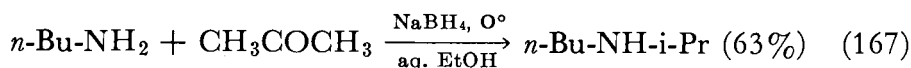
The cyano group is not as widely used as a blocking agent in the conversion of primary amines to secondary amines, owing to the objectionable

usually be nitrosated at the *para* position, giving a *p*-nitroso dialkylaniline, which is cleavable by alkali to a secondary amine and *p*-nitrosophenol (Eq. 166) (see Chapters 3 and 13). One of the few useful applications

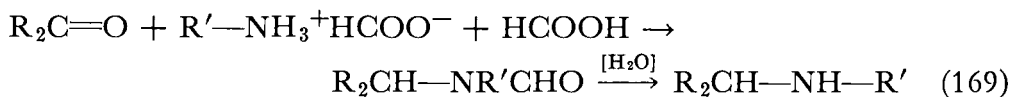


of the method is the synthesis of piperazine from ethylene bromide.

Reductive alkylation is a widely used preparative method for secondary amines.^{16, 96} Ketones, aldehydes, and oximes can be used, in conjunction with catalytic hydrogenation or reduction by sodium borohydride (Eqs. 167, 168). The most prevalent side reaction is tertiary amine formation,

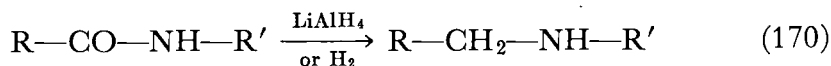


but this is usually important only when aldehydes are used. The Leuckart reaction⁸⁶ is also applicable to primary amines (Eq. 169), and accom-



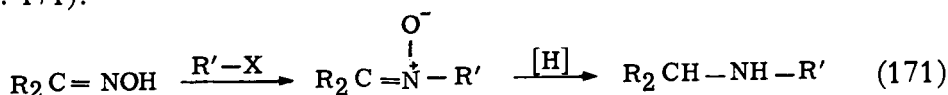
plishes their conversion to dialkylformamide, whose hydrolysis to secondary amines is a trivial step.

Among other classes of nitrogen compounds, reduction to secondary amines can be applied to N-alkyl imides, to N-alkyl amides, and to nitrones. The first of these really represents the case of reductive alkylation of primary amines with aldehydes or ketones, with isolation of the intermediate, and little more need be said about it here; there is little advantage in isolating the imines. Sodium borohydride will reduce imines without disturbing other easily reduced groups, such as nitro groups. Amides are difficult to reduce, but high-pressure hydrogenation (usually with copper chromite catalyst) is generally successful, and lithium aluminum hydride has developed into a reliable reagent for this purpose⁹⁷ (Eq. 170). Although the reduction of N-alkyl amides has wide scope,

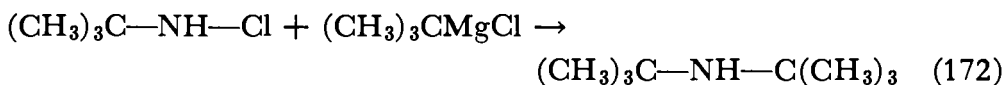


it should be borne in mind that one group in the product must necessarily be primary. The reduction of nitrones has been much less widely

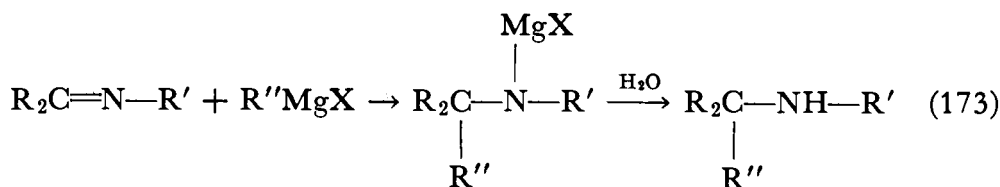
applied, largely because the nitrones are more troublesome to prepare; alkylation of oximes is the general method, but the nitrones are then always accompanied by significant quantities of their O-alkyl isomers, useless for the production of secondary amines (see Chapter 8). Catalytic hydrogenation or lithium aluminum hydride are the usual means (Eq. 171).



The Grignard reagent can be used to prepare secondary amines in two ways, but only one of them gives generally useful yields. N-Halo primary amines react with Grignard reagents, but the amounts of secondary amines formed are usually very small, oxidation-reduction being the dominant reaction (see Chapter 4). Nevertheless, for the synthesis of the highly hindered di-*tert*-butylamine (Eq. 172), it is the only reaction

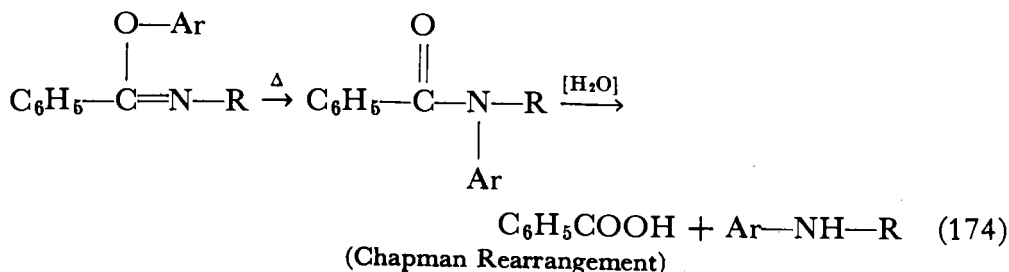


known to succeed. The addition of Grignard reagents to ketimines is a sluggish reaction, but can be made to give usable yields⁹⁸ (Chapter 7) (Eq. 173). A useful feature of the reaction is that one of the alkyl groups



of the product is tertiary. Addition sometimes fails or is very incomplete when there are hydrogens α to the azomethine carbon, for these can undergo an acid-base reaction with the organometallic reagent, producing only the metal derivative of the ketimine.

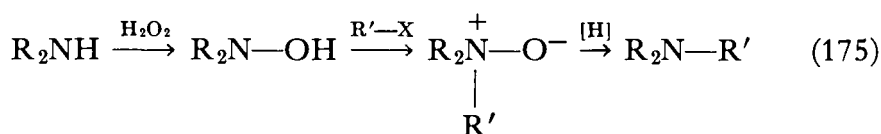
The only rearrangement reaction of significance in the preparation of secondary amines is the Chapman rearrangement, in which an N-substituted imino ester is converted to a disubstituted amide (Eq. 174). The



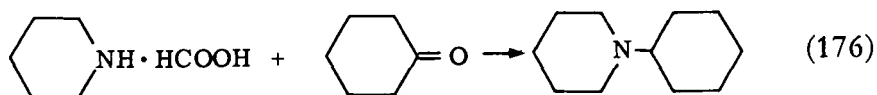
rearrangement occurs easily when an aryl group is on the oxygen, but it is extremely difficult with alkyl groups (Chapter 4).

C. Tertiary Amines

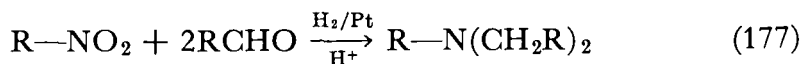
Tertiary amines can be prepared by simple alkylation, just as can primary and secondary amines. There is usually little trouble in stopping the process before quaternization, except with the smallest alkyl groups, and there is thus no strong need of a blocking group. When blocking is wanted, however, the hydroxyl group can be used. Hydrogen peroxide converts most secondary amines smoothly to dialkylhydroxylamines; these can be alkylated on the nitrogen by ordinary methods, giving tertiary amine oxides, from which the oxygen can be removed by a variety of reductive means (Chapter 8) (Eq. 175).



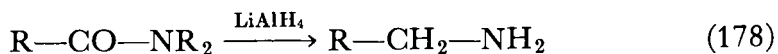
Reductive alkylation of secondary amines also gives tertiary amines. This can be carried out by means of hydrogenation, sodium borohydride,^{96b} or with formic acid, as the Leuckart reaction^{86, 99} (Eq. 176).



Reductive alkylation has been combined with reduction of nitro alkanes; when they are hydrogenated in the presence of aldehydes and acid, tertiary amines result (Eq. 177). Reduction of dialkyl amides also gives

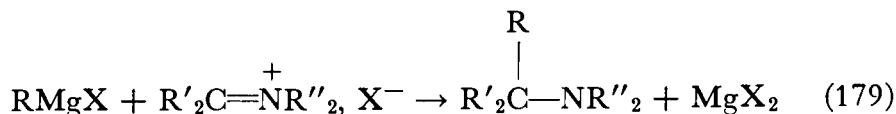


tertiary amines. Although catalytic hydrogenation and electrolysis have been used, lithium aluminum hydride has become the reagent of choice¹⁰⁰ (Eq. 178).

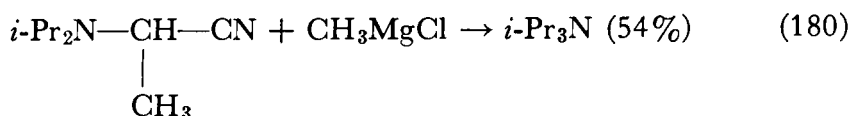


The Grignard reagent can be utilized in the preparation of tertiary amines in three ways, all of which involve the formation of new C—C bonds and the generation of a secondary or tertiary substituent. Addition to ketimmonium salts gives good yields of tertiary amines in one step, but the required salts themselves also have to be made, of course (Eq.

179). The replacement of the cyano group of α -amino nitriles by the



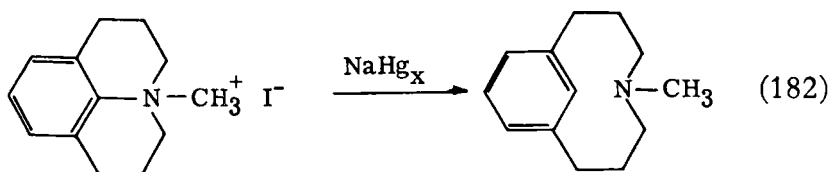
organic moiety of a Grignard reagent is known as the Bruylants reaction (Eq. 180); although yields are only moderate, it has special synthetic



application.¹⁰¹ The addition of Grignard reagents to dialkylformamides, known as the Bouveault-Bush reaction,¹⁰¹ usually gives low yields, although its simplicity is an advantage (Eq. 181).

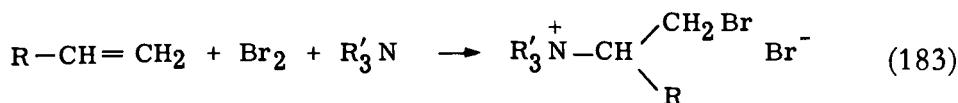


Finally, it should be mentioned that the various degradation reactions of quaternary ammonium compounds give tertiary amines, although such reactions are not usually of synthetic value, since the required quaternary compounds must usually be prepared from the tertiary amine in the first place. An exception is the complete methylation of a primary or secondary amine to a quaternary compound, followed by removal of a methyl group with lithium aluminum hydride^{71e} or sodamide.¹⁰² A special case of interest is the synthesis of a *meta*-bridged derivative by the Emde reduction (Eq. 182).

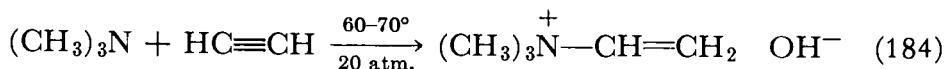


D. Quaternary Ammonium Compounds

Quaternary ammonium compounds are synthesized almost solely by alkylation of tertiary amines,¹⁰³ a reaction that has been discussed earlier in this chapter. The only variant is the use of olefins and acetylenes instead of alkyl derivatives of strong acids. Although olefins alone are for practical purposes inert toward tertiary amines, some olefins will react in the presence of strong acids, and many will react with amines while adding halogens, producing β -haloalkyl quaternary salts (Eq. 183).



Acetylenes will react simply by heating (under pressure when gaseous acetylenes are used).¹⁰⁴ The products are vinyltrialkylammonium compounds (Eq. 184), but these, of course, can be hydrogenated if a saturated



compound is ultimately wanted.

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chapter three

Aromatic Amines

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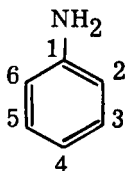
NOMENCLATURE

The title of this chapter is interpreted broadly so as to include aniline, its ring-substituted relatives, N-alkyl and N-aryl anilines, and also compounds with amino groups attached to other aromatic nuclei, such as naphthalene, pyridine, and other heterocycles. The emphasis, however, is on benzene derivatives. "Aralkyl" amines, in which an amino group is attached to a side chain, will not be taken up, since such compounds are essentially aliphatic as far as the amine function is concerned. Quinone imines, which by strict interpretation should appear in Chapter 7 (Carbonyl Derivatives), are discussed in this chapter because of the interrelationship of their chemistry with that of the aromatic diamines.

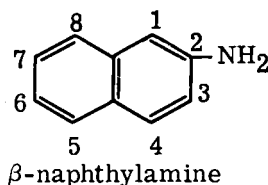
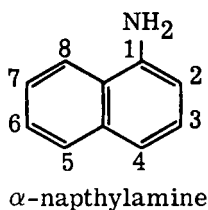
MONOAMINES

Aromatic amines are named as substituted anilines. When a benzene ring bears the amino group, the carbon holding the amino group is automatically given the number 1. When there is only one other substituent on the ring, the locant prefixes *ortho*, *meta*, and *para* may be used. With

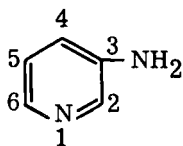
naphthylamines, the naming follows a similar course, except that the ring numbering must start with an α -position closest to the amino group.



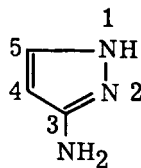
There are thus two unsubstituted naphthylamines, 1- and 2-, also known as α - and β -. The Greek letter locants should not be used when substituents are also present. Amino derivatives of larger fused-ring systems



follow similar principles. With heterocyclic systems, the name of the ring takes precedence, and the amino group is designated by a prefix just as other substituents. The numbering is, of course, fixed for each heterocyclic ring by established custom (and usually principle), which the presence of an amino group does not alter. In a few cases, Greek letter locants were once common. In the special case of the diamino deriva-

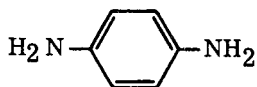


3-(or β -) aminopyridine

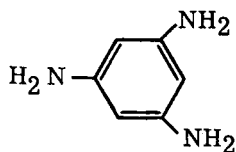


3-aminopyrazole

tives of benzene, the phenylene radical, $-\text{C}_6\text{H}_4-$, *ortho*, *meta*, or *para*, is commonly used in naming, but otherwise the amino groups of di- and poly-amines are best indicated by prefix nomenclature.



p-phenylenediamine



1,3,5-triaminobenzene

Aniline itself is one of the earliest organic nitrogen compounds to be obtained pure and have its structure determined. The name is derived from the fact that it was once obtained by destructive distillation of indigo from alkali; Fritsche coined the now international name from the Spanish word for indigo, anil, in 1840. It had actually been known since 1828 as a minor constituent of coal tar.

A. Properties

Aniline, with a boiling point of 184.4° compared to 110.6° for toluene, is clearly much involved with hydrogen bonding. Its boiling point is the lowest of any aromatic amine (if we exclude certain of its fluorine derivatives). It freezes at -6.24° , which shows that the effect of the amino group in destroying the symmetry of benzene (mp 5.5°), and thus lowering the melting point, is not quite balanced by the hydrogen-bonding forces. Methylation of the amino group does not greatly affect the physical properties. The melting and boiling points of some other aromatic amines are given in Table 3-1.

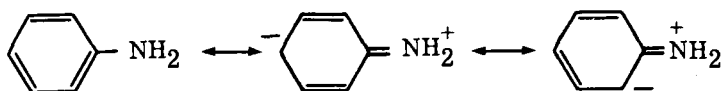
Aniline is a much weaker base than ammonia; the effect of substitution of hydrogen by an aryl group is thus opposite to the effect of alkyl substitution. The base strengths of aromatic and aliphatic amines differ by factors of 10^4 to 10^6 (i.e., 4 to 6 in pK_a). This effect is so great that two aryl groups are enough to lower the base strength of ammonia below that of water, and diaryl and triaryl amines are thus no longer basic in the ordinary sense, and will not dissolve in aqueous mineral acid.

The base-weakening effect of the phenyl group is apparently a dual influence, arising from inductive electron withdrawal and delocalization of the unshared electron pair of the nitrogen by orbital overlap with the

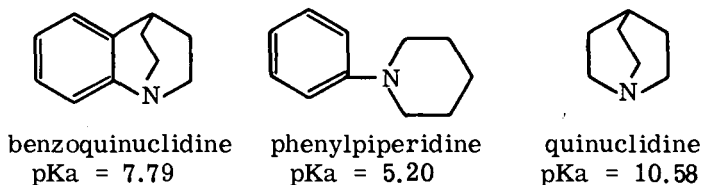
Table 3-1 *Physical properties of some aromatic amines*

Amine	mp	bp	$pK_a(\text{ArNH}_3^+)^1$
Aniline	-6.24°	184.4°	4.59
N-Methylaniline	-57	195.7	4.85
N,N-Dimethylaniline	2.5	193	5.06
<i>o</i> -Toluidine	-16.25	200.7	4.39
<i>m</i> -Toluidine	-31.5	199	4.69
<i>p</i> -Toluidine	45.7	200	5.09
α -Naphthylamine	49	301	3.92
β -Naphthylamine	112	306	4.11
α -Aminopyridine	56	204	
Diphenylamine	52.8	302	0.85
Triphenylamine	127	365	<0

pi electrons of the ring. The latter effect, often termed resonance or mesomerism, can be represented by resonance structures.



For resonance to be maximally effective, approximate coplanarity of the groups on nitrogen with the ring plane is required, a fact that makes it subject to steric influences.² Benzoquinuclidine cannot assume the required planar arrangement, and thus should be free of the mesomeric influence, and show only the inductive effect. Actually it is a much stronger base than phenylpiperidine, in which there is no steric restriction and both effects should be operative. However, benzoquinuclidine is still a markedly weaker base than quinuclidine, the fully aliphatic analogue. Wepster has interpreted these facts as indicating that the inductive and the mesomeric effects contribute roughly equally to the base-weakening influence in unhindered anilines.^{2b} The effect of alkyl-



tion on the nitrogen of aniline is mildly base-strengthening,^{1b} as shown in Table 3-1, and the drop in base strength encountered with aliphatic amines in going from secondary to tertiary amine is not observed. The basicity can be correlated by use of the Taft equation according to Hall's treatment as discussed in Chapter 2.^{1b}

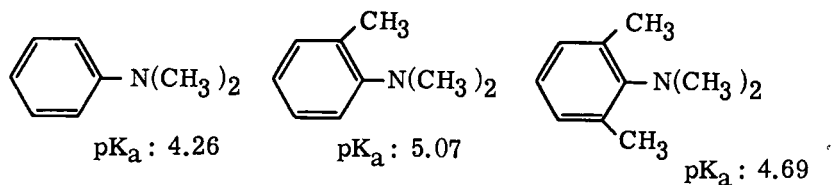
The base strength of aniline is very susceptible to the influence of substituents, owing to the pronounced ability of the benzene ring to transmit electronic effects. The effects of *meta* and *para* substituents can be correlated by the Hammett equation, $\log K/K_0 = \rho\sigma$, with a reaction constant, ρ , of -2.77 . The correlation is not as good with the ordinary substituent constants (σ) as it is with the adjusted set (σ^+) designed for use with reactions that involve a positive charge on or near the benzene ring. *Ortho* substituents, which cannot be correlated by the Hammett equation because of the large entropy effects, have a much stronger influence, a reasonable result of their closeness to the site of reaction. Some representative values are given in Table 3-2; it can be seen from these that base-weakening effects are common and pronounced, whereas base-strengthening effects are weak. The strongest open-chain aniline derivative so far reported is N,N-diethyl-*o*-toluidine, pK_a = 7.18, but it is still not as strong as benzoquinuclidine.

Table 3-2 *Base strengths of some substituted anilines (in water at 25°)*

Substituent	K_a for ArNH_3^+	$\text{p}K_a$
<i>o</i> -NO ₂	1.82	-0.26
<i>p</i> -NO ₂	1.02×10^{-1}	+0.99
<i>m</i> -NO ₂	3.45×10^{-3}	2.46
<i>o</i> -Cl	2.30×10^{-3}	2.64
<i>m</i> -Cl	4.60×10^{-4}	3.34
<i>m</i> -F	4.06×10^{-4}	3.39
<i>p</i> -Cl	1.50×10^{-4}	3.82
<i>m</i> -CH ₃ O	6.31×10^{-5}	4.20
<i>o</i> -CH ₃	4.04×10^{-5}	4.39
<i>o</i> -CH ₃ O	3.18×10^{-5}	4.49
<i>p</i> -F	2.95×10^{-5}	4.53
H	2.54×10^{-5}	4.59
<i>m</i> -CH ₃	2.03×10^{-5}	4.69
<i>p</i> -CH ₃	0.81×10^{-5}	5.09
<i>p</i> -CH ₃ O	0.51×10^{-5}	5.29

Calculated from the data of M. Kilpatrick and C. A. Arenberg, *J. Am. Chem. Soc.*, **75**, 3812 (1953), and N. F. Hall and M. R. Sprinkle, *ibid.*, **54**, 3469 (1932).

The base strengths of *ortho*-substituted anilines are subject to steric as well as electronic influences; two different types of steric effect have been proposed. The base strength of dimethylaniline is increased by a single *o*-methyl group from $\text{p}K_a$ 4.26 * to $\text{p}K_a$ 5.07,* but a second *o*-methyl group reduces the basicity again, to $\text{p}K_a$ 4.69.* The explanation offered ^{3a} is that there is steric interference between the tetrahedral nitrogen and the *o*-methyl groups in all rotational positions, which thus raises the potential energy of the ammonium ion relative to the amine more than enough to counterbalance the inductive effect of the added methyl group.



The other type of steric effect, often called steric inhibition of resonance or conjugation, is shown by the result of N-methylation on picramide (2,4,6-trinitroaniline). Picramide is, of course, an extremely weak base, owing to the combined influence of three nitro groups. N,N-Dimethyl-

* These values were measured in 50% ethanol solution, and should not be compared with those in Tables 3-1 and 3-2, which are for aqueous solution.

picramide,^{3b} however, is stronger by nearly five powers of ten. It has been proposed in explanation that a large part of the base-weakening effect of the nitro groups is due to conjugative interaction with the amino group, which requires coplanarity of the amino group, nitro groups, and the benzene ring for maximum effectiveness. The introduction of methyl groups on the nitrogen would be expected to reduce such conjugation drastically, since a coplanar structure would be of very high energy owing to the extensive steric interference between the methyl groups and the oxygen atoms of the *ortho* nitro groups.

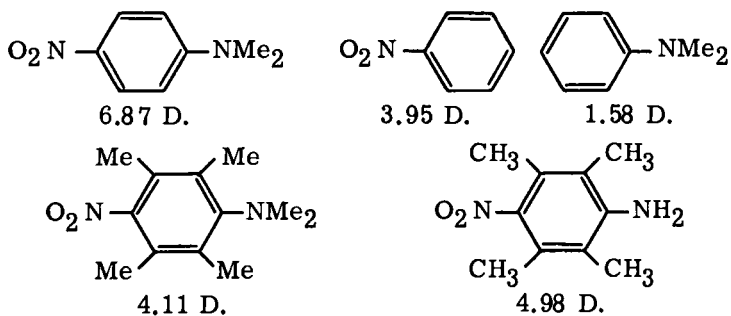
Primary and secondary aromatic amines are acidic as well as basic, although the acidity is almost always less than that of water. They readily react with Grignard reagents to form magnesium salts, as do primary and secondary aliphatic amines. Monoaryl amines are not very reactive toward alkali metals, however, and do not react with alkali metal alkoxides appreciably. Diarylamines are close to alcohols in their acidity, and may form potassium salts readily, as in the case of carbazole. Substitution of the benzene ring with nitro groups increases the acidity, of course, and three nitro groups make picramide (2,4,6-trinitroaniline) a feeble acid even in the presence of water.

The solubility of arylamines follows the ordinary generalizations; aniline itself shows borderline solubility in water at room temperature (*ca.* 4%), and will itself dissolve water (*ca.* 5%). Other solutes may greatly affect the solubility, in predictable directions. Inorganic salts exert the customary salting-out effect, when they do not form complexes; alkali carbonates and hydroxides are particularly effective. Salts of organic acids or bases may have the opposite effect, and increase the solubility. Substitution, except by obviously hydrophilic groups such as hydroxyl and amino, nearly always decreases solubility.

The electronic interaction of the amino group with the benzene ring and with substituents on it also affects other properties⁴ besides basicity. The atomic refraction of an individual atom in a molecule can be calculated from molar refractions if it is assumed that such atomic refractions in general remain constant from one molecule to another, in other words, that they are additive. The atomic refractions can be taken as a guide to the electronic condition of the atom, a high value indicating a loosely held electron cloud.^{4b} The value for nitrogen in most tertiary anilines (e.g., dimethylaniline) is smaller than that for tertiary aliphatic amines; this has been attributed to *pi*-orbital overlap with the ring, as discussed in connection with basicity.^{4a} When an amino group is prevented by steric effects from becoming coplanar with the ring, such conjugation should be largely ineffective. Such a case is 2,6,N,N-tetramethylaniline (2-dimethylamino-*m*-xylene), the atomic refraction of whose nitrogen approaches that of aliphatic tertiary amines.^{5a} The same phenomenon

is seen in effects on the chemical shifts in C^{13} nuclear magnetic resonance^{5b}; steric inhibition of conjugation shows up as deshielding at the *ortho* and *para* ring carbons in *ortho*-substituted N,N-dimethylanilines. Similarly, the ultraviolet spectra of simple alkyl anilines show a moderately intense maximum near 2500 Å, attributed to a $\pi \rightarrow \pi^*$ transition of the conjugated system. This band becomes progressively weakened in intensity as steric interference with coplanarity is increased.^{4a}

Dipole moments have also been used to investigate the interaction between an amino group and a benzene ring with its substituents.^{4a, 6} Since a dipole moment is a product of electric charge and the distance of separation, and interatomic distances do not vary greatly, differences in dipole moment are a useful guide to inequalities in electron distribution within a molecule. Essentially all amines, aliphatic and aromatic, have a measurable dipole moment, since the amine structure is not in general planar. For aniline, this moment amounts to 1.53 Debyes, and for dimethylaniline, 1.58 D. When another group responsible in its own right for a dipole moment is in the *para* position to an amino group, the resulting moment may be the vector sum of the separate moments, but in some cases it is considerably more. This has been attributed to mesomeric interaction. *p*-Nitrodimehtylaniline, for example, has a dipole moment of 6.87 D., compared to 5.04 D., the value calculated from the moments of nitrobenzene and dimethylaniline (the moment of dimethylaniline is taken as lying along a line inclined 38° to the Ar-N axis since the molecule is not planar). When the interacting groups are prevented from becoming coplanar with the ring, this effect disappears; thus 1-dimethylamino-4-nitrodurene has a dipole moment of only 4.11 D. We have altogether five important properties of aromatic amines—basicity, electronic spectrum, molar refraction, nmr chemical shift, and dipole moment—affected by the electronic interaction of the amino group. We shall see presently that more obviously chemical properties, such as orienting power, are also affected.



It is worth emphasizing that aniline and most of its relatives are toxic in one way or another. The destructive action of aniline on the red corpuscles of the blood has been known for a long time. The special

danger to the chemist arises from the fact that aniline is used widely in the laboratory, and can be absorbed through the skin as well as through breathing the vapors. Other arylamines, notably β -naphthylamine, have been found to be tumor-inducing. It is obvious that these compounds should be handled with conscious care.

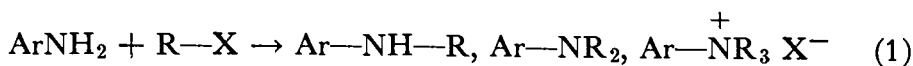
B. Reactions

SALT FORMATION Salt formation is, of course, the simplest and most general reaction of aromatic amines. Because of the lower basicity of aromatic amines, their salts are easily dissociated by heating, and are often extensively hydrolyzed in solution. The salts with weak acids, such as acetic, may depart widely from the general characteristics of salts, and they often show quite low melting points. Aniline acetate itself has not been crystallized at all; a crystalline double salt, $\text{ONH}_2 \cdot 2\text{AcOH}$, mp 16.7° , is known, however.

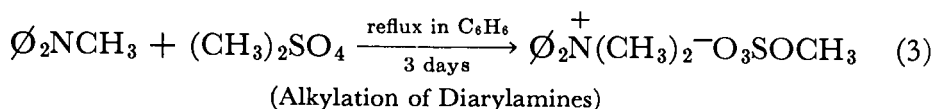
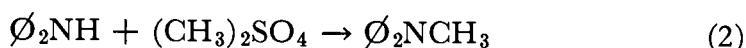
Picrates are of special value in handling aromatic amines, for even when the amine is such a weak base that other salts are unstable, picrates are usually well defined. This appears to be due to the ability of the picryl group to form charge-transfer complexes with the amines when conventional salt formation fails ⁷ (see Chapter 14). An acidic hydroxyl group is not actually necessary, and aromatic amines form charge-transfer addition products reversibly with many aromatic nitro compounds. Aniline and nitrobenzene immediately form a red oil, and aniline and 1,3,5-trinitrobenzene form deep red leaflets, mp $123\text{--}124^\circ$, when mixed in alcoholic solution.

Anilide salts of active metals, such as ONH^- , Na^+ or $(\text{ONH}^-)_2\text{Mg}^{++}$, are formed from arylamines and the free metals, their amides or hydrides, or organometallic compounds.⁸

ALKYLATION Alkylation of aromatic amines with the usual alkylating agents occurs more or less readily ⁹; alkylation is also possible in the vapor phase (usually *ca.* 400°) with alcohols over alumina or other catalysts, but such processes are usually confined to industrial use. With small, reactive alkylating agents, difficulty is encountered in stopping alkylation cleanly at the secondary amine stage, and quaternization is usually possible when steric crowding is not too great (Eq. 1).

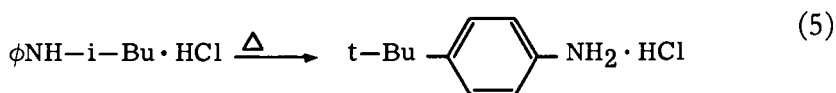
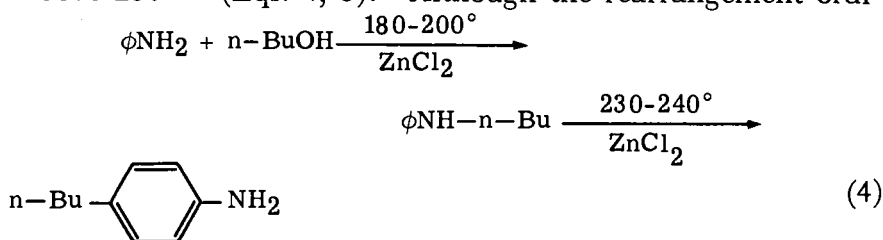


Diarylamines are very slow to alkylate, as would be expected from their low basicity. Nevertheless, diphenylamine and methyldiphenylamine have been successfully methylated with methyl sulfate, *p*-toluenesulfonate, or iodide ¹⁰ (Eqs. 2, 3). Sodium or magnesium salts of diarylamines



are more easily alkylated, even with alkyl chlorides.^{10e} Triarylamines do not react at all with alkylating agents.

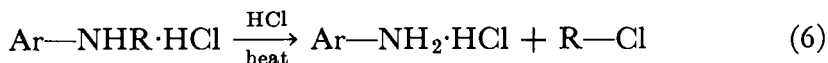
DEALKYLATION A potential competing reaction with alkylation is the Hofmann-Martius rearrangement, by which an alkyl group migrates from nitrogen to the *ortho* and *para* positions on the ring. The conditions required are simply heating of an alkylarylamine salt, usually at temperatures above 250°¹¹ (Eqs. 4, 5). Although the rearrangement ordi-



(Hofmann-Martius rearrangement)

narly proceeds by dissociation to carbonium ions, with Wagner-Meerwein rearrangement of the migrating alkyl group from a primary to a secondary or tertiary structure, migration occurs without rearrangement in the zinc-chloride-catalyzed reaction, whose mechanism is thus presumably different.^{11d}

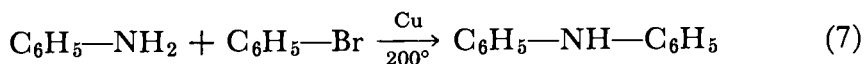
N-Alkylation is, of course, reversible, as it is with alkylamines. Heating N-aryl ammonium salts therefore nearly always results in some dealkylation if the alkyl groups are not part of a ring. If the heating is conducted in a current of hydrogen chloride, removal of alkyl groups may be complete¹² (Eq. 6). The mechanism is apparently a bimolecular



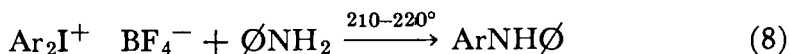
displacement on the alkyl groups, since *n*-propyl groups are removed mostly as *n*-propyl halide.

ARYLATION Aromatic amines, particularly primary, may also be arylated.^{11, 13} Aryl halides with strongly electron-withdrawing groups, such as nitro, *ortho* or *para* to the halogen react the most easily, and with two or more such activating groups may approach the reactivity of alkyl halides. Poorly activated aryl halides can still be induced to react with amines, however, with the use of a copper catalyst and high enough temperatures (>200°); under such conditions, the process is sometimes

called an Ullmann reaction (Eq. 7). Diphenylamine itself can be pre-

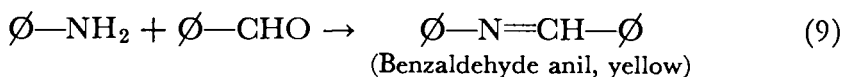


pared in this way from aniline and bromobenzene (cf. the Dow process for the synthesis of aniline from chlorobenzene and ammonia). Diaryliodonium fluoborates have also been used as arylating agents ^{13b} (Eq. 8).

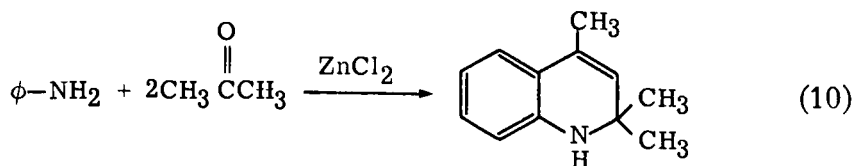


Furthermore, arylation has also been accomplished with phenols in the presence of certain Lewis-acid catalysts, such as zinc chloride, and with amine hydrochlorides. The latter provides the simplest route to diphenylamine: heating aniline with its hydrochloride above 200° (and therefore under some pressure). Naphthols are more active arylating agents than phenols in such reactions; they can also be used as arylating agents in a slightly different way, in the Bucherer reaction with bisulfite as catalyst (see the section on synthetic methods).

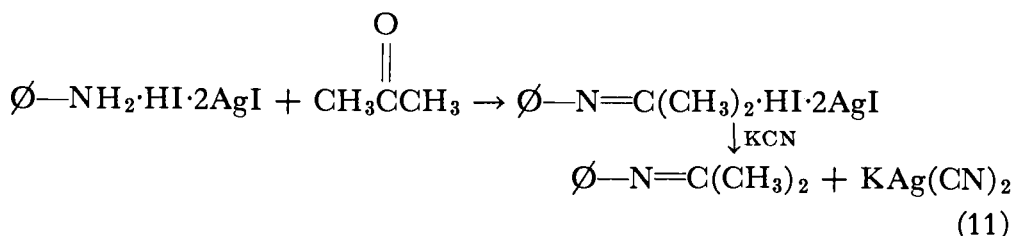
ALDEHYDES AND KETONES Aldehydes and ketones react with aromatic amines much as they do with aliphatic amines, with the added complication that the reactive *ortho* and *para* positions of the ring may become involved. With primary amines, reaction is nevertheless mostly on nitrogen. Elimination of water from the carbinolamine first formed occurs especially easily when benzaldehydes are used,¹⁴ being aided by the conjugation possible in the products, known as anils or Schiff's bases (Eq. 9). The corresponding reaction with ketones is much more sluggish



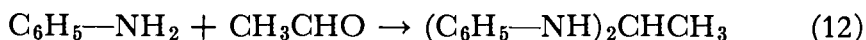
than that with aldehydes and usually requires acid catalysis (Lewis acids, such as zinc chloride, are often used). Attempting to force the reaction of aniline with acetone by such means was the origin of an involved misidentification in the literature. A crystalline substance obtained by Knoevenagel from acetone and aniline was widely accepted as acetone anil for many years, and its reactions were studied as typical of anils. It was not until 1932 that Reddelien and Thurm¹⁵ showed that the supposed "acetone anil" was in reality a dihydroquinoline, resulting from reaction of two moles of acetone and cyclization to an *ortho* position (Eq. 10). True acetone anil was subsequently made by the much milder



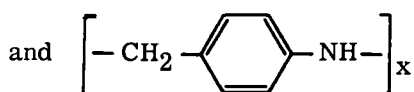
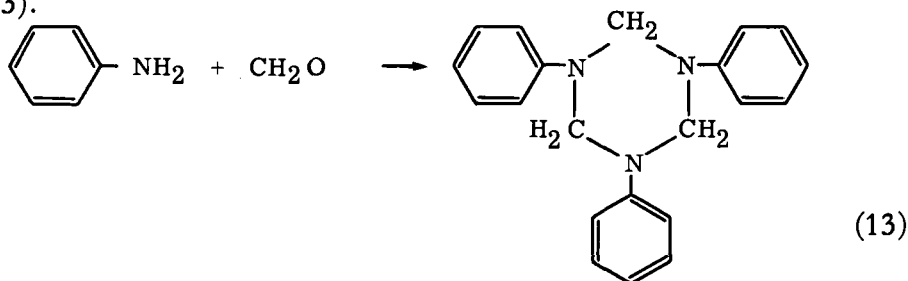
technique of allowing anilinium iodide-silver iodide adduct, $\text{C}_6\text{H}_5\text{NH}_2\cdot\text{HI}\cdot 2\text{AgI}$, to react with cold acetone ¹⁶ (Eq. 11).



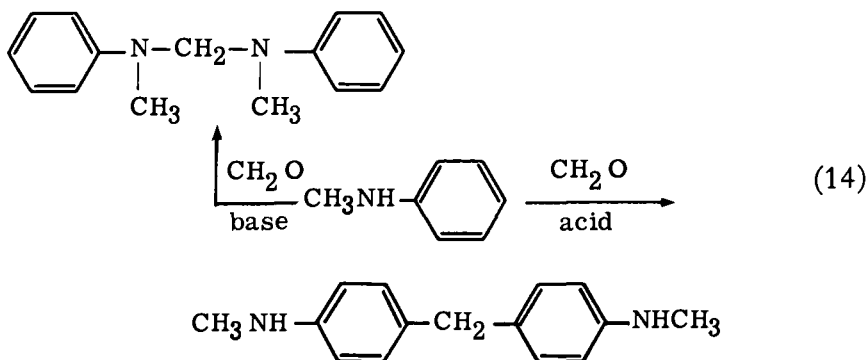
Aliphatic aldehydes are likely to form *gem*-diamines by reaction with two moles of aniline ¹⁸ (Eq. 12), and reaction at the *para* position is more



likely to be a competing reaction. Reaction at both sites gives polymers (Eq. 13).



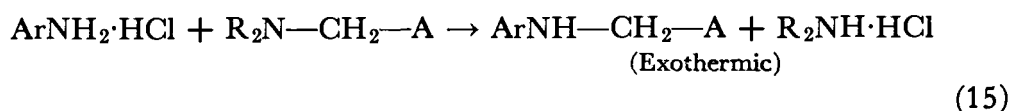
With secondary and tertiary aromatic amines, Schiff's bases obviously cannot form. Condensation with the ring and *gem*-diamine formation can both occur with secondary amines, as shown by the reactions of *N*-methylaniline with formaldehyde ^{18c} (Eq. 14). In basic medium, a



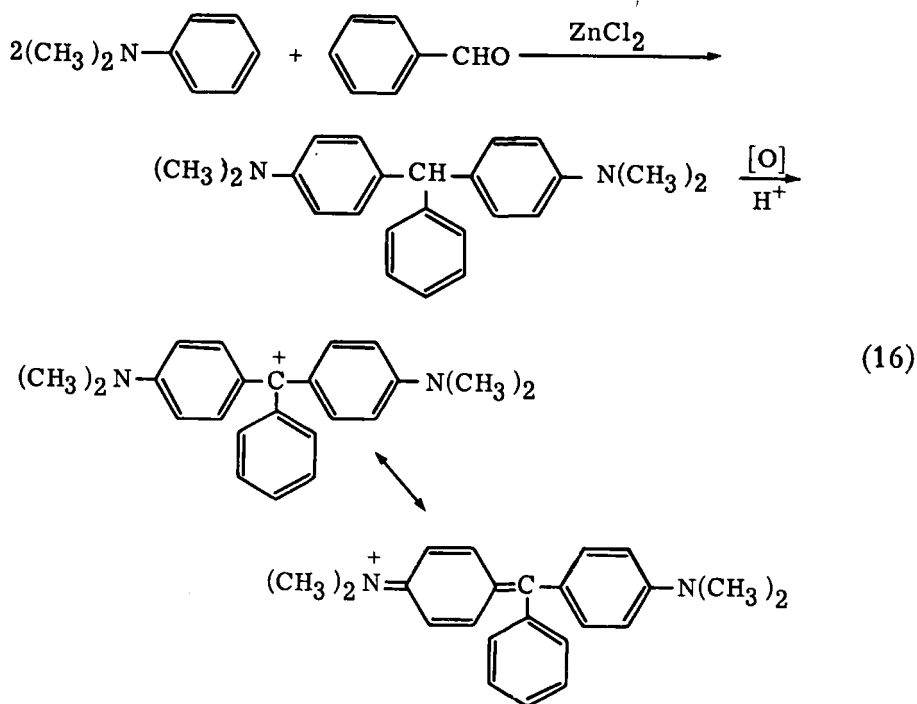
methylenediamine derivative is formed by reaction at the nitrogen; in acid solution, a diphenylmethane derivative is formed by reaction at the

para position. The difference is presumably due to the nature of the attacking species, molecular CH_2O in base, and cationic derivatives, such as CH_2OH^+ or $\text{ArRN}^+=\text{CH}_2$, in acid. Trimeric compounds $(\text{R}-\text{N}-\text{C}_6\text{H}_4-\text{CH}_2-)_3$ have also been obtained from N-alkyl anilines

and formaldehyde in the presence of acid; their structure is essentially established by the fact that zinc in sulfuric acid reduces them to *p*-toluidines. N-Aryl Mannich bases can obviously not be expected to be prepared in the ordinary way from formaldehyde and an active hydrogen compound; they have, however, been prepared indirectly by an amine-exchange reaction with aliphatic Mannich bases ¹⁹ (Eq. 15).

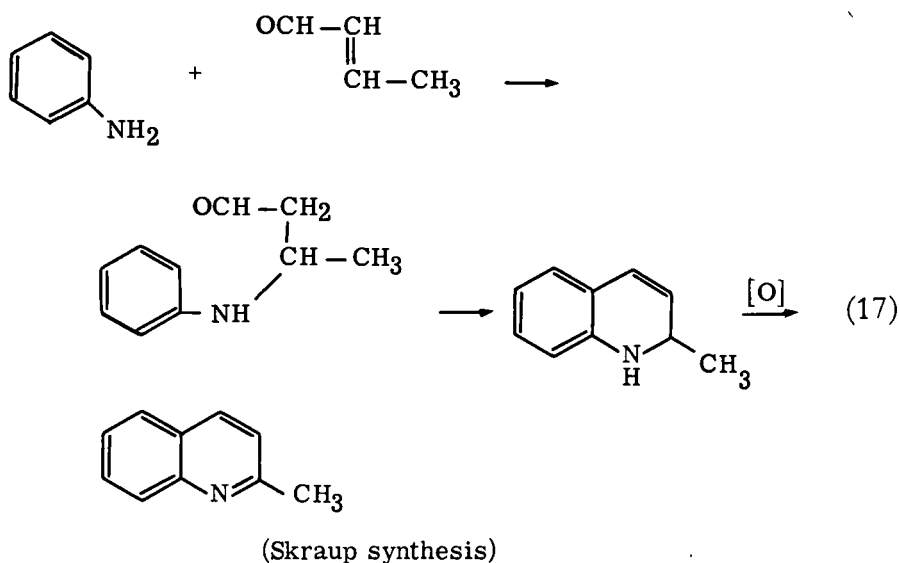


With tertiary amines, ring condensation becomes the exclusive reaction; it is acid-catalyzed.²⁰ This is the basis of the important synthetic reactions leading to the triarylmethane dyes. Benzaldehyde and dimethylaniline, for example, give malachite green when warmed with zinc chloride and then oxidized ²¹ (Eq. 16).



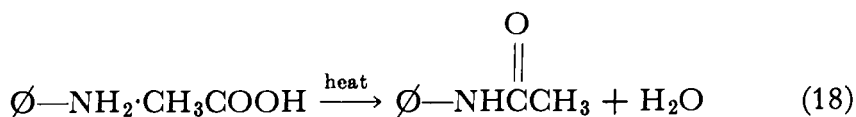
The reaction of primary aromatic amines with α, β -unsaturated aldehydes or ketones (or substances easily convertible to them) in the presence of an oxidizing agent is the well-known Skraup synthesis of quinolines.²²

The initial reaction is actually an alkylation of the amino group by the olefinic double bond, as shown by the fact that crotonaldehyde gives 2-methylquinoline and not the 3-isomer (Eq. 17). Acid-catalyzed



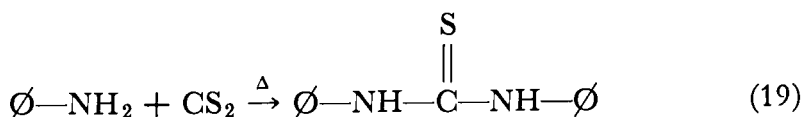
cyclization to the *ortho* position follows to give a dihydroquinoline, which is dehydrogenated by the oxidizing agent (usually nitrobenzene).

ACYLATION Acylation of primary and secondary aromatic amines proceeds so similarly to acylation of aliphatic amines that little more need be said here. The same reagents generally accomplish the same reactions under the same conditions. The resulting amides are usually named as anilides. Ring acylation does not ordinarily occur. Acylation by heating aniline salts of carboxylic acids is usually a cleaner reaction than with aliphatic amines, and the higher boiling point of aromatic amines, which prevents their escape during heating, makes the reaction convenient to carry out ^{14, 23} (Eq. 18). Excessive heating, however, can convert the

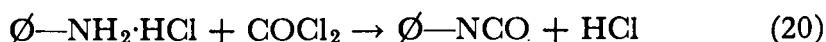


anilides to diaryl amidines.

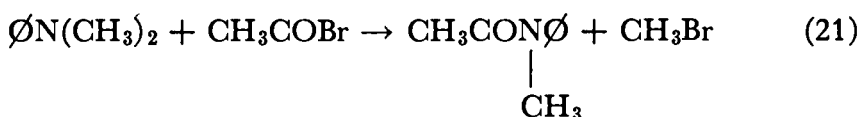
The reaction of aromatic amines with carbon disulfide is slightly different from that of aliphatic amines, in that reaction is easily carried beyond the dithiocarbamate stage to symmetrical thioureas ²⁴ (Eq. 19).



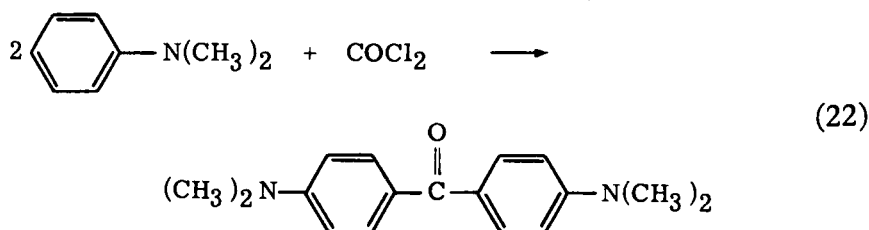
Only when a stronger base is also present, such as ammonia or alkalies, can dithiocarbamates be isolated. Phosgene converts primary aromatic amines (or their salts) smoothly to isocyanates (Eq. 20).



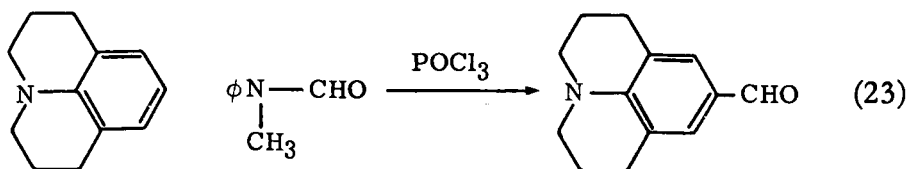
Tertiary aromatic amines, which cannot be acylated to amides, are often inert to acylating agents, but they may react at the nitrogen to produce N-acyl quaternary salts, which may subsequently undergo alkyl group cleavage if acyl bromides are used (Eq. 21), presumably owing to



the greater nucleophilicity of bromide ion (cf. the von Braun cyanogen bromide reaction, Chapter 6). Another possibility is ring acylation, as exemplified by the formation of aryl phosphines with phosphorus trichloride, and the important dye intermediate, Michler's ketone, from phosgene and dimethylaniline (Eq. 22); ring acylation often proceeds



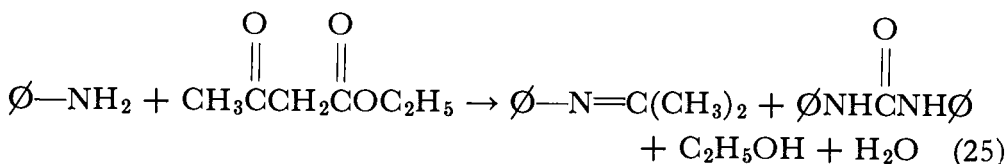
poorly, however.²⁵ Formylation, using formanilides in the presence of phosphoryl chloride, is the useful synthetic procedure known as the Vilsmeier-Haack reaction²⁶ (see Chapter 4) (Eq. 23).



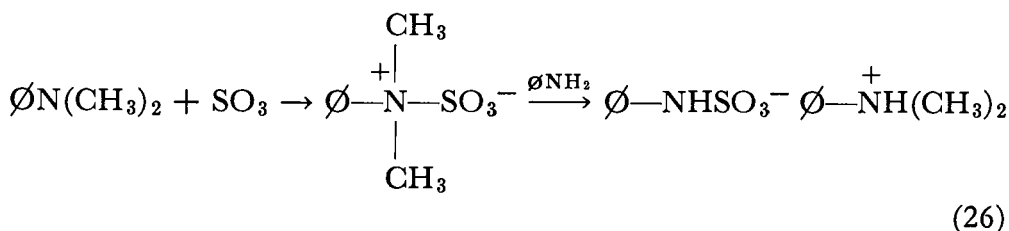
Esters are not ordinarily reactive toward secondary and tertiary aromatic amines, but primary amines can be acylated to anilides at high enough temperatures²⁷ (Eq. 24). Acetoacetic ester will undergo solvo-



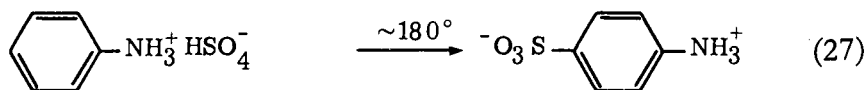
lytic decarboxylation ("ketone cleavage") if heated sufficiently strongly with aniline²⁸; the products are the aniline analogues of acetone and carbonate, the ordinary products of cleavage by aqueous alkali (Eq. 25).



Thionyl chloride behaves analogously to phosgene, and gives thionyl-anilines (thionyl-N-phenylimines),²⁹ $\text{Ar--N}=\text{SO}$. Chlorosulfonic acid in cold chloroform, and potassium fluorosulfonate in aqueous-alcoholic alkali, attack primary and secondary amino groups, producing sulfamic acids³⁰ (isolated as their salts); N-sulfonation is also brought about by reaction with amine-sulfur trioxide adducts, such as dimethylaniline-sulfur trioxide. These substances are formed by direct action of sulfur trioxide vapor on tertiary amines of all sorts (Eq. 26).



Nuclear substitution, on the other hand, is accomplished by sulfuric acid.³¹ In the strongly acidic solutions usually needed for sulfonation with sulfuric acid, the amino group of most anilines is completely protonated, so that reaction is slow and *meta* substitution is significant (cf. the discussion of nitration that follows). When the *para* position is already occupied, *meta* sulfonation usually becomes the dominant reaction. The simplest expedient to obtain *para* sulfonation of aniline is to protect the amino group by acetylation, which keeps sufficient of the amino compound unprotonated so as to allow *para* sulfonation to take place. There is another useful alternative, however. The amine bisulfates can be heated in the solid state and thus converted to *para* (or *ortho*) sulfonic acids (Eq. 27). At the temperatures required, it can be antici-

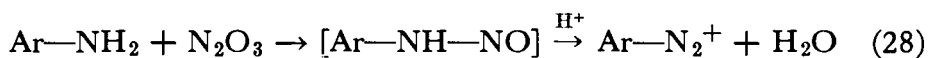


pated not only that the salt will be somewhat dissociated into amine and acid, but also that the sulfuric acid will be somewhat dissociated into water and sulfur trioxide. These two phenomena would be sufficient to account for the observed sulfonation. It is a commercial process important in the production of dye intermediates, of which the simplest example is sulfanilic acid (aniline-*p*-sulfonic acid, actually almost entirely a zwitterion).

Of all the acylating agents for aromatic amines, the most important (and the most involved) are nitrous acid and related nitrosating agents.³²

They attack primary, secondary, and even tertiary amines, and the products in each case have important chemical behavior of their own. The chemistry of the nitrosamines derived from secondary amines and of the C-nitroso compounds derived from tertiary amines will be discussed later on (Chapters 15 and 13). The chemistry of the diazonium salts, derived from primary aromatic amines, will be taken up in Chapter 11.

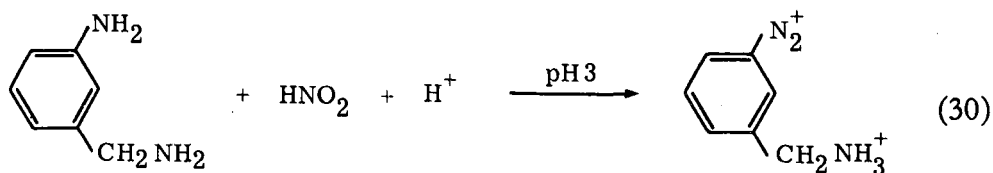
NITROUS ACID Primary aromatic amines react with solutions of nitrous acid to give diazonium salts, ArN_2^+X^- , or their decomposition products. If the diazonium salts are not to decompose almost as soon as they are formed, the solutions must usually be kept ice-cold. The reaction is apparently not essentially different from that of aliphatic amines, the superficially large differences being a matter of the relative stability of the aromatic diazonium species on the one hand, and the additional possibilities of rearrangement and elimination present in the aliphatic members, on the other. The actual diazotization processes are kinetically similar, in both cases involving a molecule of the free base reacting with an active nitrosating species (Eq. 28).



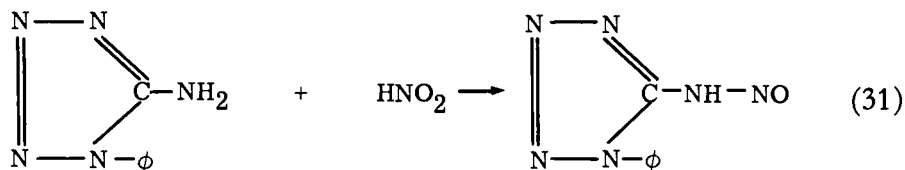
The kinetic order observed in a given experiment depends on the relative concentrations of the free base and the several possible nitrosating species; the ordinary case shows a third-order kinetic law (Eq. 29). It

$$\frac{-d(\text{ArNH}_2)}{dt} = k(\text{ArNH}_2)(\text{HNO}_2)^2 \quad (29)$$

is clear that extremely concentrated acid may prevent diazotization altogether by tying up the amino group too thoroughly in the form of the inert conjugate acid. Very weak bases, however, can be diazotized in the presence of quite concentrated acid, so incompletely protonated are they. Since even the strongest aromatic amines are much weaker than aliphatic, it is possible to adjust the acidity so that aliphatic amines are protected from nitrous acid by overwhelming protonation, while enough free aromatic amine remains to permit diazotization. In this way it has been possible to diazotize *m*-aminobenzylamine without destroying the aliphatic amino group ³³ (Eq. 30).

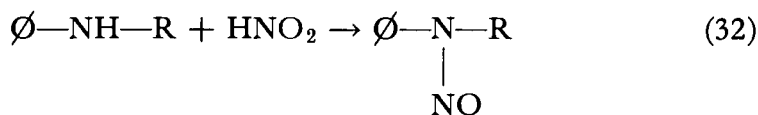


In a few cases, especially among heterocyclic compounds, the dehydration step fails, and primary nitrosamines are the final products ³⁴ (Eq. 31).



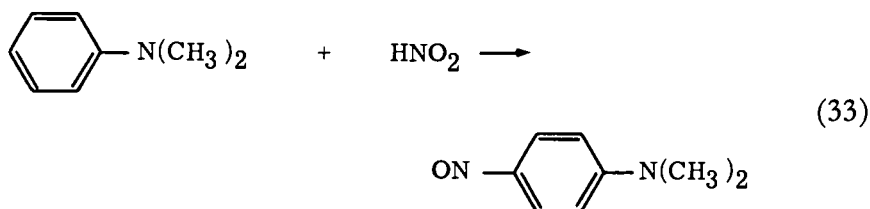
1-Phenyl-5-aminotetrazole is a case in point. 5-Aminotetrazole itself also gives an isolable nitrosamine, but it can be converted to a diazonium salt in strongly acid solution.

Secondary aromatic amines give nitrosamines just as do their aliphatic analogues; both diaryl and alkyl aryl types do this (Eq. 32). Subsequent

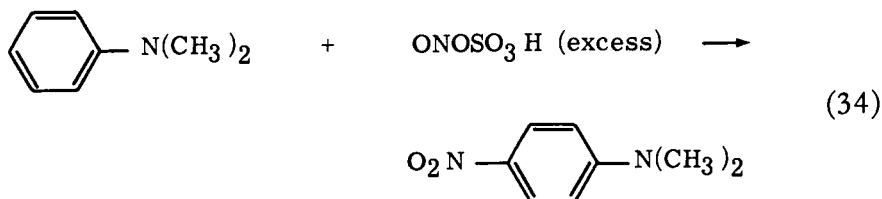


reactions that may occur, such as the Fischer-Hepp rearrangement, are discussed in Chapter 15.

Tertiary aromatic amines may undergo several types of reaction with nitrous acid. The simplest of these is C-nitrosation on the *para* position of the ring; with dilute nitrous acid and dimethylaniline, this is the principal reaction (Eq. 33). An oxidation step may follow, converting the



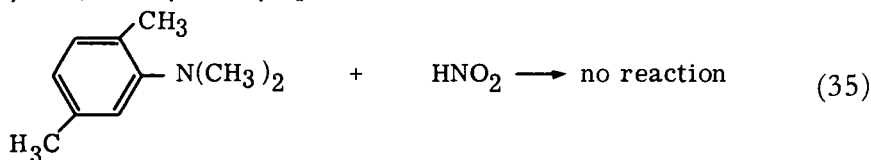
nitroso group to a nitro group ^{32, 35} (compare nitrous acid-catalyzed nitration, Chapter 14) (Eq. 34). Oxidation by nitrous acid (or a species



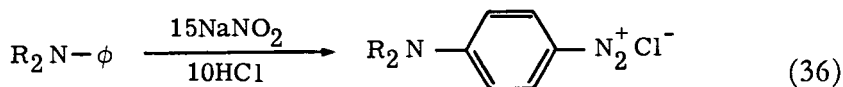
in equilibrium with it) is not confined to action on the nitroso compounds, but may also take place on the original amine. Highly colored substances, perhaps arising through oxidative coupling to a benzidine system, are produced.

The reactivity of dialkyl anilines toward nitrosation appears to depend on the ability of the dialkylamino group to approach coplanarity with

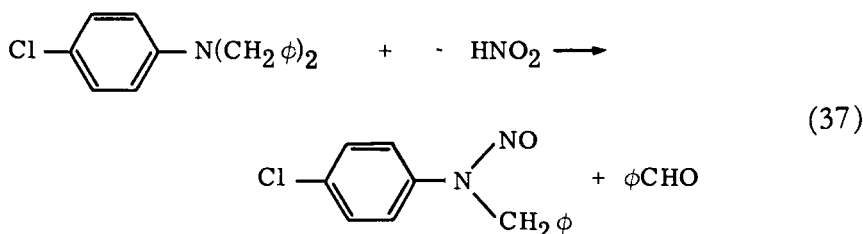
the benzene ring, for the presence of an *ortho* substituent, as in dimethyl-amino-*p*-xylene, nearly always prevents nitrosation (Eq. 35), as does also



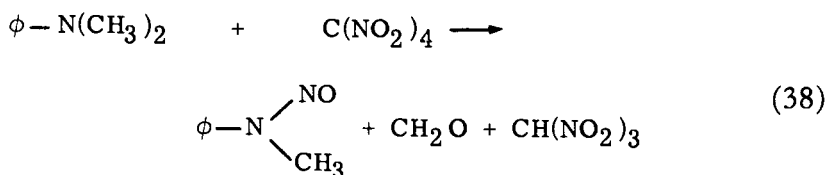
the presence of a *tert*-butyl group on the nitrogen.³⁶ It was originally reported that dialkyl anilines bearing groups larger than propyl do not give *p*-nitroso compounds, but the assertion has since been demonstrated to be incorrect.³⁷ The use of *p*-nitrosodialkylanilines in the synthesis of secondary amines is mentioned in Chapters 2 and 13. When a very large excess of nitrous acid is used, the end product is a diazonium salt³⁷ (Eq. 36).



When attack on the benzene ring is prevented by substitution, the tertiary amino group may be attacked instead. An alkyl group is cleaved off in an oxidized form, usually aldehyde, and the resulting secondary amine subsequently becomes nitrosated^{38a,b,c} (Eq. 37) or even

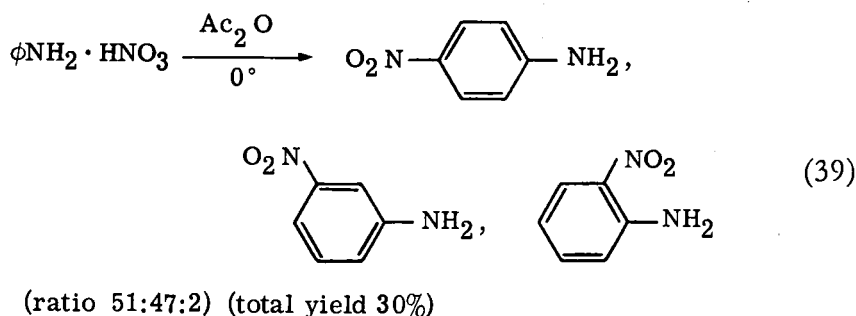


nitrated.^{3d, 38d} Such steps may occur in the manufacture of the explosive, Tetryl (N,2,4,6-tetranitro-N-methylaniline), by the action of excess nitric acid on dimethylaniline, a somewhat complex process. The mechanism of alkyl group cleavage by nitrous acid is presumably similar to that operating in the analogous reaction with aliphatic amines (see Chapter 2). Tetranitromethane also replaces alkyl groups by nitroso, even when a *para* position on the ring is available³⁹ (Eq. 38).



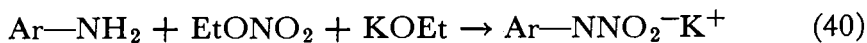
Nitrating agents affect aromatic amines principally by attacking the ring when used in acidic media. An amino group on a benzene ring greatly activates it toward nucleophilic attack, and nitration would occur

rapidly were it not for the protonation of the amino group. The ammonio group, $-\text{NH}_3^+$, has the opposite influence on the ring, and in addition to being deactivating, is weakly *meta*-directing. As a result, mixtures of nitroanilines are produced, whose composition depends on both the nitrating agent and the acidity of the medium.⁴⁰ In strongly acidic solutions, reaction is slower, and the principal products are *meta*- and *para*-nitroanilines.^{40a} Nitration by treatment of anilinium nitrate with acetic anhydride produces mostly the *ortho* isomer, although only in modest yield (Eq. 39).



Nitration of aniline is, however, often complicated by a competing oxidation, which may give colored products related to quinone. For this reason, nitration of anilines is not generally employed for synthetic purposes, but instead, the amino group is protected by acylation (usually acetylation, but also phthaloylation and benzenesulfonylation). This reduces the sensitivity of the ring to oxidation, suppresses polynitration by moderating the vigor of the reaction (the acylamido group is less powerfully activating), and avoids the incursion of *meta* substitution by keeping the amino group essentially unprotonated. At the same time, however, the exceptionally strong *ortho*, *para*-directing power of the amino group is weakened, as a result of which the orienting power of other groups that may be present can exert a greater influence.

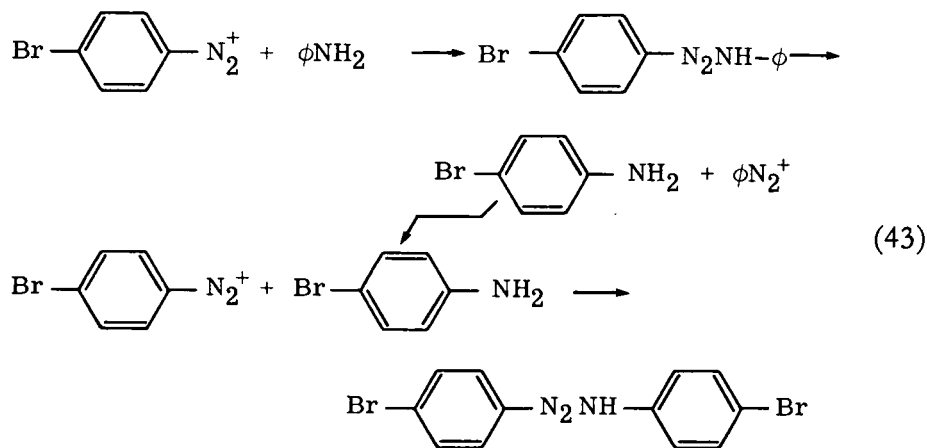
Nitration of aromatic primary amines can also be accomplished by alkyl nitrates in the presence of strong base, but under these conditions, it is the amino group that is the site of reaction.⁴¹ The products are aryl nitramines, isolated as their salts (Eq. 40). The reaction presumably



proceeds by nucleophilic attack by anilide anion on the nitrate ester nitrogen atom. Such a process suggests why aliphatic amines, which are much less readily converted to anions, are not converted to nitramines by similar treatment.

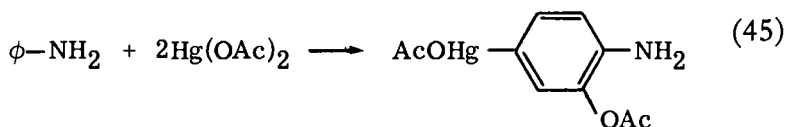
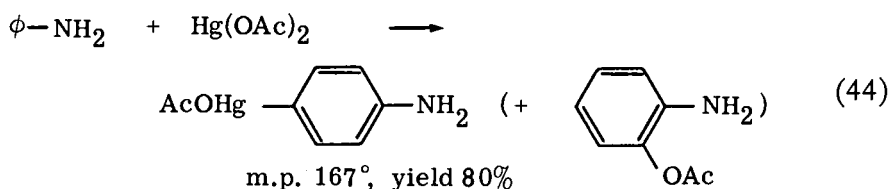
Aqua regia completely destroys the aniline system, converting it to

to occur, so that a mixture of symmetrical and unsymmetrical coupling products may eventually be obtained. *p*-Bromobenzenediazonium chloride and aniline, for example, give both *p*-bromodiazooaminobenzene and *p,p'*-dibromodiazooaminobenzene (Eq. 43).



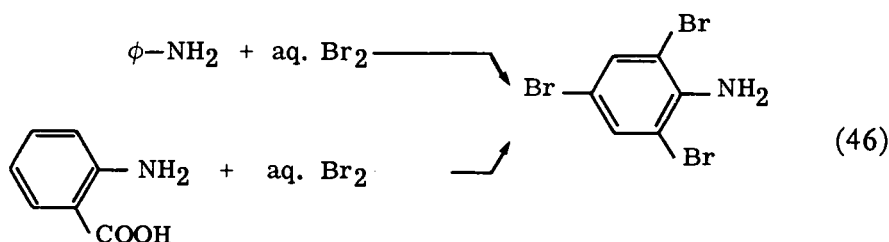
Tertiary amines, of course, cannot give a stable product by coupling at the amino group, and aminoazo compounds are thus the only products. As with nitrosation and halogenation, coupling is more difficult with *N,N*-dialkylanilines bearing an *ortho* substituent that interferes with the formation of a coplanar system. Similarly, when the presence of a *para* substituent forces diazo coupling to occur at an *ortho* position, the reaction is much more difficult.

MERCURATION Mercuration of aromatic amines may give rise to co-ordination compounds, their elimination products (*N*-acetoxymercuri compounds), or ring-substituted products.⁴⁴ Nuclear mercuration, usually with mercuric acetate, is brought about easily by gentle warming in alcoholic solution. The formation of the unstable *N*-mercuri compounds appears to be relatively fast, and is then followed by a slower ring-substitution reaction. Aniline is converted by mercuric acetate either to monosubstituted products (*p*-acetoxymercuri- plus a little *ortho* isomer) or to 2,4-*bis*(acetoxymercuri)aniline (Eqs. 44, 45), although with



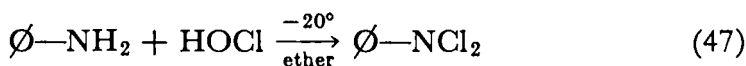
proper care, impure $\phi\text{NH}_2 \cdot \text{Hg}(\text{OAc})_2$ and $\phi\text{NHHgOAc}$ can be isolated. Mercuric halides give an array of compounds by reaction with aromatic amines, but none of them appear to be ring-substitution products.

HALOGENATION Halogenation of aromatic amines occurs exceptionally easily unless strongly deactivating substituents are also present. In water solution, the halogenation of aniline is so rapid that it cannot be feasibly stopped before the introduction of three halogen atoms, filling up the *ortho* and *para* positions.⁴⁵ The reactions are quantitative, and, because of the insolubility of the trihaloanilines produced, can be used as sensitive test reactions for either aniline or free halogen. Electron-withdrawing substituents, such as halo, sulfo, and carboxyl, are often displaced during halogenation if they occupy an *ortho* or *para* position⁴⁶ (Eq. 46). Halogenation can be moderated in solvents less polar than



water, such as glacial acetic acid or carbon tetrachloride, however, and monohalo products can often be obtained.⁴⁷ On the other hand, addition as well as substitution has been claimed for chlorination under more drastic conditions, giving octachlorocyclohexanone N-chloroimine.⁴⁸

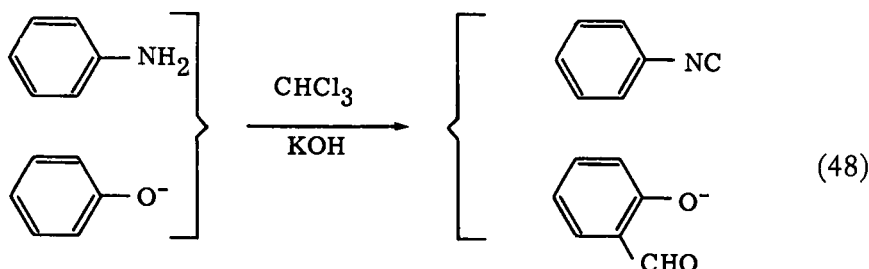
N-Chlorination has been accomplished by treating aniline with hypochlorous acid in cold ether⁴⁹ (Eq. 47). The product, N,N-dichloro-



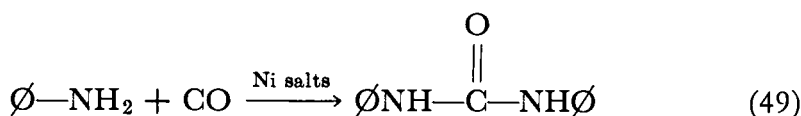
aniline, is very unstable, and is rapidly converted to ring-chlorinated compounds.

DIVALENT CARBON The "carbylamine reaction," the formation of an isocyanide by treatment with chloroform and strong alkali, occurs readily with aromatic primary amines, and can even be a useful synthetic method (see Chapters 2 and 5). It is interesting to compare this reaction with the action of the same reagents on the electronically similar phenols (Eq. 48). In this, the familiar Reimer-Tiemann reaction, an entirely different type of product, an aldehyde, is formed, resulting from attack on carbon instead of the oxygen atom.

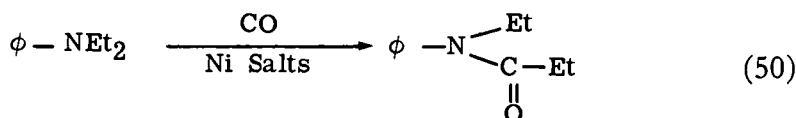
Carbon monoxide reacts with anilines in an entirely different manner⁵⁰ from chloroform. In the presence of "carbonylation catalysts" (various



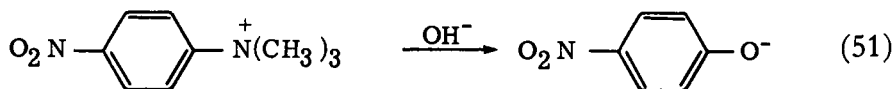
nickel salts), primary aromatic amines are converted to diaryl ureas (Eq. 49). Tertiary aromatic amines, such as diethylaniline, surprisingly



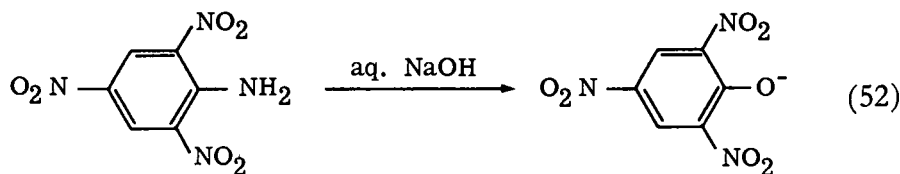
undergo insertion of a carbonyl group between an alkyl group and nitrogen, producing secondary amides (Eq. 50).



HYDROLYTIC CLEAVAGE The C—N bond in most aromatic amines, as with aliphatic, is ordinarily inert to hydrolysis, except in the quaternary ions, where an alkyl group may be displaced by hydroxide ion (see Chapter 2). Electron-withdrawing groups *ortho* or *para* to an amino group greatly increase the susceptibility of the ring to attack by nucleophilic species, however, and *p*-nitrophenyltrimethylammonium ion, for example, is cleaved by alkali largely to *p*-nitrophenol⁵¹ (Eq. 51). It is possible

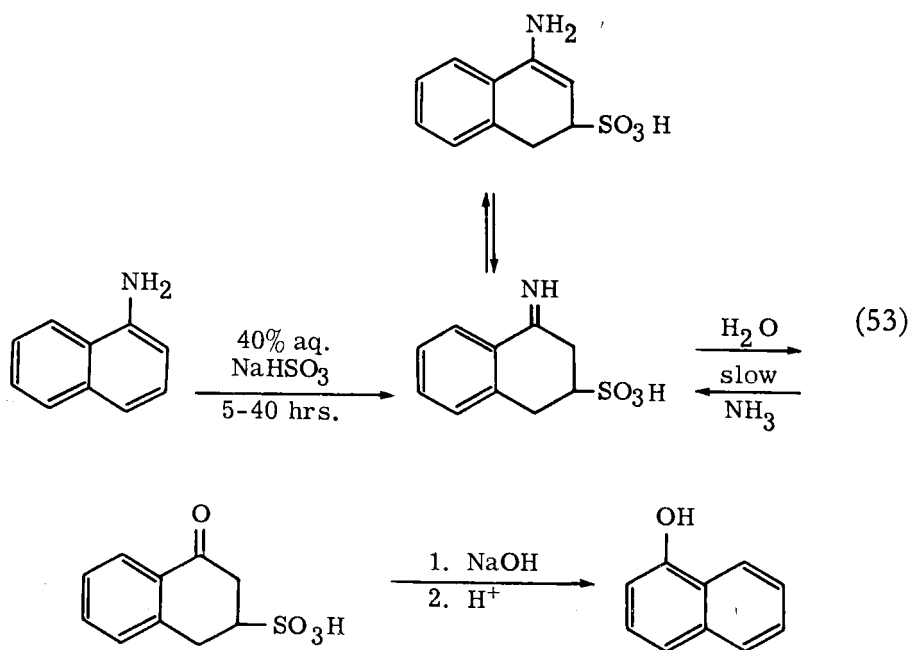


to hydrolyze *ortho*- and *para*-nitroanilines to phenols by drastic treatment with alkali.⁵² Three co-operating nitro groups, such as found in picramide (2,4,6-trinitroaniline) make the amino group as easily hydrolyzable as in many carboxamides (Eq. 52). This is, of course, only



one aspect of the general phenomenon of nucleophilic substitution on the benzene ring. Heterocyclic aromatic amines, such as the α - and γ -aminopyridines, show similar behavior without the need of electron-withdrawing substituents.

The exchange of an aromatic amino group (primary or secondary) for a hydroxyl group can in some cases be effected by the reverse of the Bucherer reaction, in which sodium bisulfite acts as a catalyst.⁵³ This reaction is largely confined to naphthylamine derivatives, in which it has commercial application in the dyestuff industry. It proceeds through isolable intermediate sulfite-naphthylamine addition products, which must be cleaved in a separate step. These compounds were long thought to be α -amino- and α -hydroxy sulfonic acids, analogous to simple carbonyl-bisulfite addition compounds, but it has recently been shown that they do not display any of the chemical behavior to be expected of such structures. Instead, a carbonyl group adjacent to a methylene group has been demonstrated to be present by both chemical and spectrographic means. The intermediates are tetralonesulfonic acids (or the ketimine analogues), resulting from the addition of bisulfite to the latent unsaturation of the naphthalene system⁵⁴ (Eq. 53). The reverse reaction is dis-

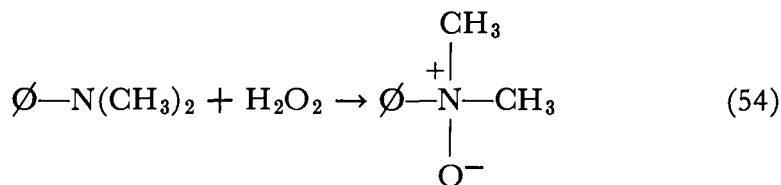


cussed in the section on preparative methods. The replacement of an amino group by hydroxyl through diazonium salts is discussed in Chapter 11.

OXIDATION Aromatic amines are as a rule quite sensitive to oxidation. This is evidently a result of the electron availability in the system,

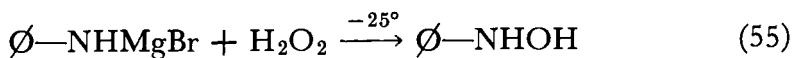
and is accordingly opposed by electron-withdrawing substituents, such as nitro. Anilines and naphthylamines lacking such substituents usually become tinted orange, pink, or violet on standing in air. The reactions occurring are complex, however, and may involve quinones, free radicals, and condensation reactions. In this connection it is interesting to recall that the first synthetic dyes were prepared by oxidizing mixtures of anilines and toluidines. It is also possible to add oxygen directly to the amino group; just as with aliphatic amines, hydrogen removal and oxygen addition are favored by different oxidizing agents, and the products ultimately obtained depend strongly on the experimental conditions. Oxygen addition will be taken up first.

Oxygen addition to the aromatic amino group requires reagents of the peroxide type, but not all of these are successful. Tertiary amines, such as dimethylaniline, can be converted to amine oxides by hydrogen peroxide or peroxy acids, such as peroxybenzoic, in a reaction quite parallel to that of aliphatic tertiary amines⁵⁵ (Eq. 54). The process



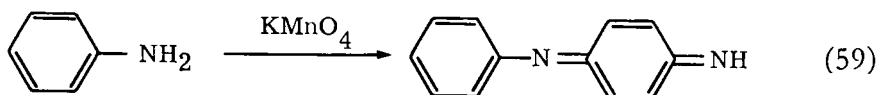
converts a nearly planar amino system to a tetrahedral one, and is understandably more difficult in cases where such a structural change introduces strains; it of course always destroys conjugation involving the unshared electron pair of the amino group.

The same reagents that convert tertiary amines to amine oxides may convert secondary amines to hydroxylamines, but with N-alkyl anilines, more deep-seated oxidation, with cleavage of the alkyl group, producing nitrobenzenes, etc., has been observed.⁵⁶ The initial step of adding oxygen apparently occurs with primary amines also, but the arylhydroxylamines that would be produced are themselves so easily oxidized that they can usually be obtained only in small quantities from such reactions; phenylhydroxylamine can be obtained, however, from the magnesium salt of aniline and anhydrous hydrogen peroxide at -25° ⁵⁷ (Eq. 55).

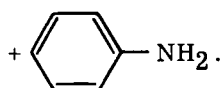


Oxidation to the nitroso stage is the usual result, and reaction of anilines with peroxymonosulfuric acid (Caro's acid), H_2SO_5 , peroxyacetic, or peroxytrifluoroacetic acid, is a preparatively useful synthesis for many

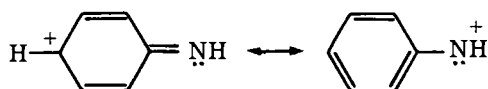
oxidation of aniline by permanganate (Eq. 59). The mechanism of



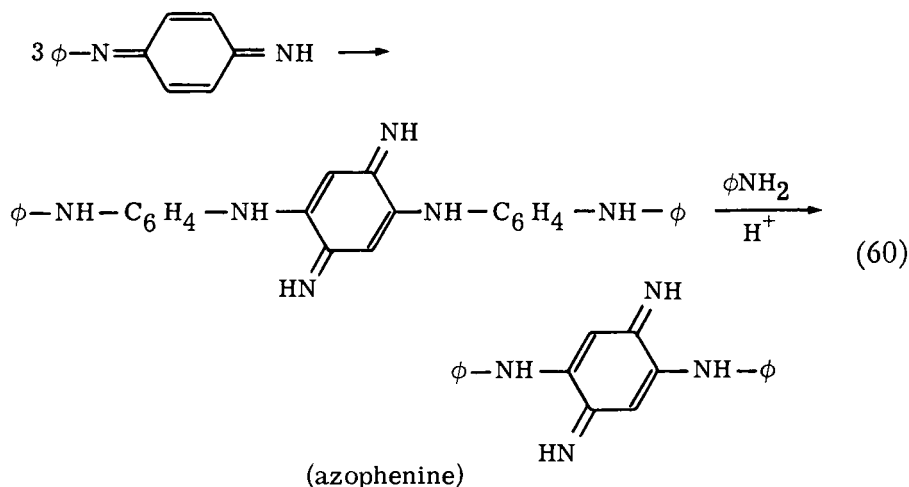
its formation has been suggested to involve an azene intermediate, $\text{C}_6\text{H}_5\text{—N:}$; this may either condense with another molecule of aniline to give *p*-aminodiphenylamine, which is then further oxidized, or it may dimerize directly. These routes appear doubtful in view of the fact that thermal decomposition of phenyl azide, which should give the same intermediate, gives quite different products when conducted in aniline solution (see Chapter 10). On the other hand, support for the concept is found in the fact that similar products have been obtained from the dehalogenation of *N,N*-dichloroaniline with copper.⁴⁹ The conjugate acid of the azene,



(or a copper chloride complex of it) offers greater likelihood of engaging in condensation reactions; it could be formed by abstraction of hydride from the amino group. Alternatively, hydride might be removed from the *para* position, giving the isomeric cation,

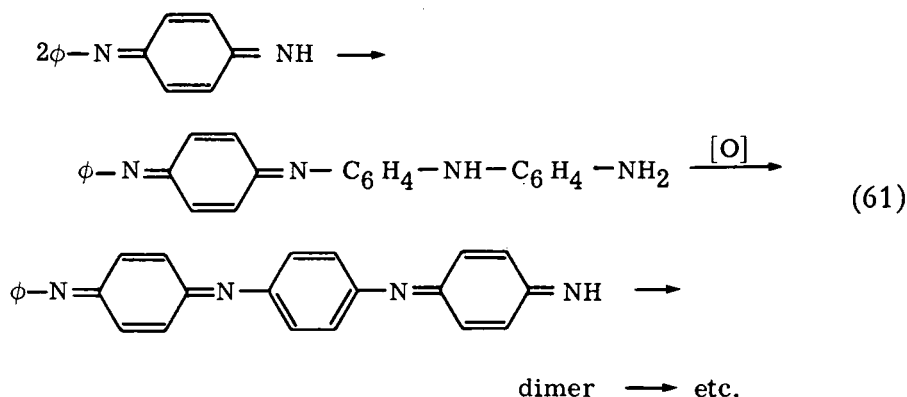


N-Phenylquinonediimine is easily trimerized by acid; in the presence of aniline, the trimer is converted into azophenine (Eq. 60), which is



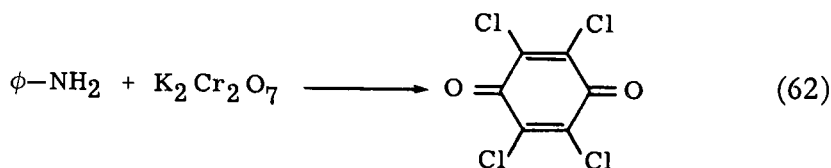
itself capable of further transformations. Under slightly different conditions of acidity, dimerization occurs; the dimer may become oxidized to

a *bis*(quinonediimine), which in turn can dimerize and then become oxidized, and so on (Eq. 61). The result is an intensely colored poly-



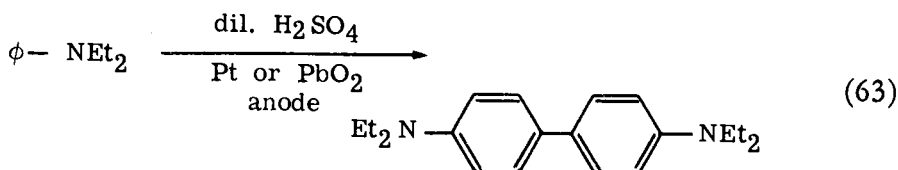
meric quinonediimine, called perinigraniline; it can be partially or completely reduced, reversibly, to *p*-phenylenediamine derivatives, which are colored in varying degrees. The structural arrangement is that of an indamine, the analogue of the indophenols, qv, p. 127. Oxidation (accompanied by hydrolysis) ultimately gives quinone in synthetically usable yield. The size of the eventual polymer(s) is unknown. Another polymeric oxidation product, known as aniline black, is of importance as a dye. It can be formed by further oxidation of partially reduced perinigraniline ("emeraldine") in the presence of aniline, and is believed to have undergone cyclization to form a polymeric chain of phenazine units.

Oxidation of aniline with aqueous chlorine or with oxidizing agents in hydrochloric acid solution ⁶² gives chloranil (Eq. 62), hence the name,



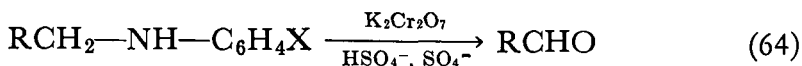
despite the fact that it is tetrachloroquinone and contains no nitrogen.

Another type of oxidation product is encountered in the anodic oxidation of *N,N*-dialkyl anilines. Carbon-carbon condensation occurs at the *para* position, possibly through intermediate free radicals, to produce tetraalkylbenzidines ⁶³ (Eq. 63).



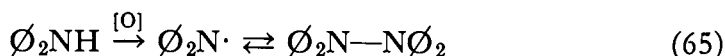
Aromatic amines bearing other substituents, especially in the *para* position, may be expected to follow different courses on oxidation, which may involve alteration or even cleavage of the other substituents. The

oxidation of N-alkyl *p*-substituted anilines, for example, can be conducted so as to cleave off the N-alkyl group as an aldehyde ⁶⁴ (Eq. 64). The

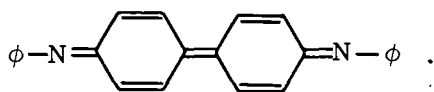


subject of oxidation of substituted anilines can become very complex, and it will not be pursued further here.

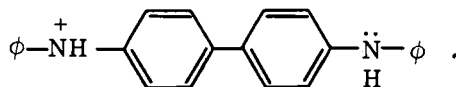
Diarylamines, typified by diphenylamine, show a distinct behavior on oxidation. The hydrogen atom is removed from the nitrogen, generating a free radical that equilibrates with its dimer, tetraphenylhydrazine ⁶⁵ (Eq. 65). In strongly acid solution, ⁶⁶ however, the cation radical



$\phi_2\text{NH}\cdot^+$ is formed, and condenses to N,N'-diphenylbenzidine or an intensely blue biphenyl derivative, an oxidized state of N,N'-diphenylbenzidine that stands between it and the weakly colored fully oxidized form, diquinone dianil,

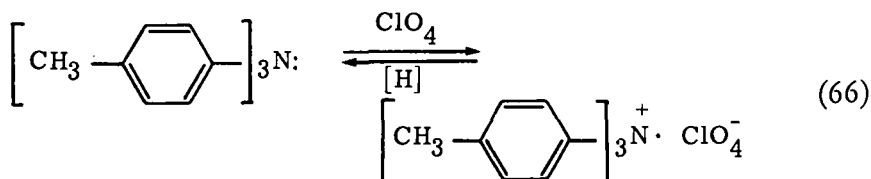


It is apparently analogous to the so-called Würster's salts, and is thus probably a free radical of nitrogen,



Because of the intensity of the color and the ease of the reaction, diphenylaminesulfonic acid, chosen for its water solubility, is useful as an indicator for redox titrations. ⁶⁷

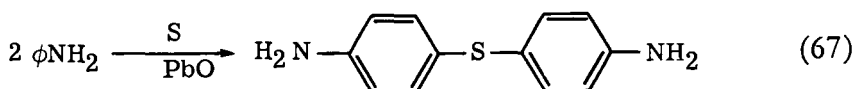
Triphenylamine responds to oxidation similarly to diphenylamine, and a colored oxidized form of tetraphenylbenzidine is formed. When all the *para* positions are blocked, however, oxidation attacks the nitrogen only, removing one electron and leaving a cation radical, ⁶⁸ a triaryl derivative of $\cdot\text{NH}_3^+$ (Eq. 66). These ions, which are deep blue, are rapidly



converted back to the parent amines by reducing agents. They are iso-electronic with the triarylmethyl radicals, but are distinguished from

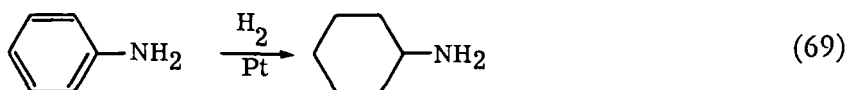
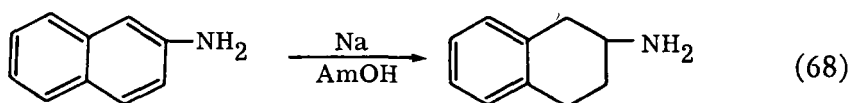
them in an important way by the presence of a positive charge; the electrostatic repulsion of like charges is, of course, a strong deterrent to dimerization. The simplest example of such oxidation occurs when tri-*p*-tolylamine is treated with chlorine tetroxide or with bromine.

Oxidation of aromatic amines can also be accomplished with sulfur. The reaction is a sluggish one, however, and is really an electrophilic substitution. *o,o'*-Diaryl sulfides are formed with sulfur alone, but interestingly, when lead oxide is added as a hydrogen sulfide acceptor, the orientation is changed, and the *para* isomer predominates ⁶⁹ (Eq. 67).



When the reaction is applied to diphenylamines, the sulfide is formed in a cyclic fashion, producing phenothiazines.⁷⁰

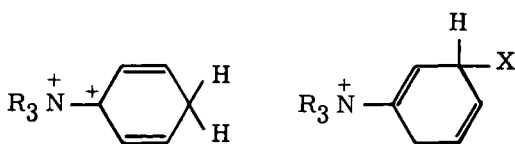
REDUCTION Reduction of aromatic amines is not ordinarily an important reaction. Hydrogenation of the benzene ring can, of course, be accomplished by conventional means, and is a useful preparative method for cyclohexylamines ⁷¹ (Eqs. 68, 69).



QUATERNARY AMINES Quaternary ammonium salt reactions are very similar for aromatic and aliphatic amines; the hydroxides of both are strong bases. Hofmann elimination and nucleophilic displacement of alkyl groups occur normally, without any unusual effect by the aryl group; the discussion of these reactions in Chapter 2 should therefore be referred to. Emde degradation by various reductive means also occurs normally (see Chapter 2); the aryl-to-nitrogen bond is commonly cleaved.

The trialkylammonio group, R_3N^+ , has an entirely different effect on the aromatic ring to which it is attached than does the uncharged amino group. It is strongly electron-withdrawing, and thus deactivates the ring toward electrophilic attack, and is largely *meta*-directing.^{40a, 72} This effect has been mentioned before in connection with substitution reactions on the ring of anilines in strongly acidic solution, where the amino group is present almost solely as the ion, $\text{Ar}-\text{NH}_3^+$. Since there are no unshared electron pairs left on the nitrogen, the group is fully

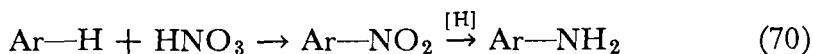
saturated and cannot be expected to take part in conjugation; its effect on the aromatic ring must therefore be entirely inductive. Nevertheless, contrary to earlier belief, phenyltrimethylammonium ion undergoes some *para* substitution (11% for nitration).^{40a} The fact that electrophilic substitution occurs almost exclusively at the *meta* positions shows that an alternating polarity has been imposed on the aromatic ring in effect. The commonly accepted explanation for this is that the transition state for electrophilic substitution can be written as a dihydrobenzene structure that distributes a positive charge to the positions *ortho* and *para* to the site of the attack. Such a transition state would clearly be of higher energy when the positive charge must be distributed to a position already holding a positively charged ammonio group.



(representation of transition states for *para* and *meta* attack on a quaternary aniline derivative)

C. Preparation of Monoamino Aromatic Compounds

Although most of the methods described in Chapter 2 for the synthesis of aliphatic primary amines have their counterparts in the synthesis of aromatic amines, the emphasis is entirely different. One method, nitration and reduction, dominates the field in aromatic chemistry (Eq. 70).

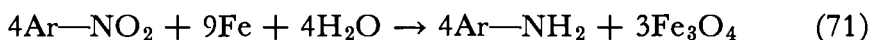


The decisive reason for this difference is that whereas nitration of all but the simplest aliphatic compounds gives mixtures of positional isomers, accompanied by fragmentation of the carbon skeleton and often extensive oxidation, nitration of aromatic compounds usually gives largely one positional isomer (or a small number) and is subject to little interference by side reactions.

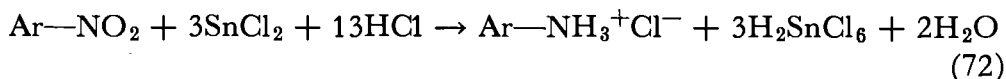
Nitration requires an acidic medium, but beyond that it is not safe to generalize, for the conditions depend so much on the compound being nitrated. For aromatic hydrocarbons, "mixed acid," a mixture of concentrated sulfuric and nitric acids, is commonly used, but with more reactive aromatic compounds, milder reagents, such as nitric acid in glacial acetic acid, are often used. Since nitration is subject to the usual orientation rules for electrophilic aromatic substitution, the position taken

by the entering nitro group can usually be predicted, and not every positional isomer can be obtained. Since the position of the amino group eventually obtained by reduction is determined by the nitration process, this is the most important limitation of the nitration-and-reduction synthesis. The preparation of nitro compounds and the mechanism of the reaction are discussed in Chapter 14.

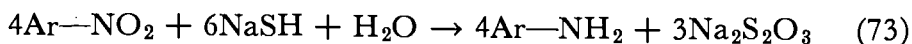
Reduction of aromatic nitro compounds is a reaction with a long history, and an enormous variety of methods have been used.⁷³ It was for a long time the only commercial synthesis for aniline. Metals that dissolve in hydrochloric acid are widely used; iron ⁷⁴ is cheap and effective, and is favored commercially, but zinc ⁷⁵ and tin ⁷⁶ are also used. The latter metals require an excess of acid, which makes the eventual isolation of the aromatic amine more cumbersome; these metals may also cause side reactions, particularly the attachment of a chlorine to the aromatic ring (see Chapter 14). With iron, only a catalytic quantity of acid need be used, and the amine is then produced as the free base and with a minimal side reaction (Eq. 71).



Salts of lower valence states of transition metals, particularly stannous ⁷⁷ and titanous ⁷⁸ chlorides, are also widely used (Eq. 72).

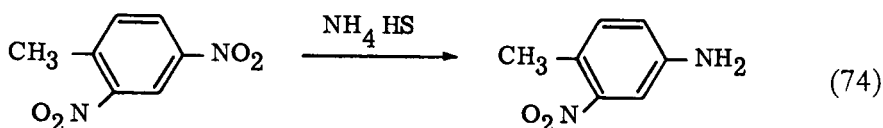


Catalytic hydrogenation, usually at room temperature and with only moderate pressure, is sometimes an effective means of reduction; palladium, platinum,⁷⁹ or nickel ⁸⁰ are the usual catalysts. Most basic reducing agents reduce aromatic nitro compounds incompletely and produce dimeric products, and are thus unsuitable for the preparation of amines. There are, however, some important exceptions. When hydrazine is decomposed catalytically in the presence of nitro compounds, the latter are reduced to amines, presumably by transient diazene (diimide, $\text{HN}=\text{NH}$); see Chapter 1. Soluble sulfides ⁸¹ or polysulfides,⁸² usually sodium or ammonium, are also effective in reducing nitro to amino groups in basic solution (Eq. 73). A valuable characteristic of ammonium



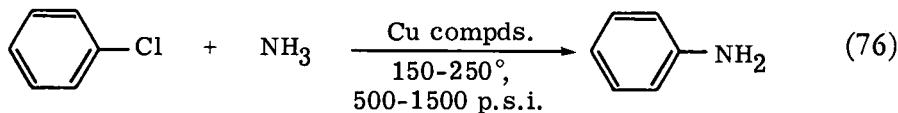
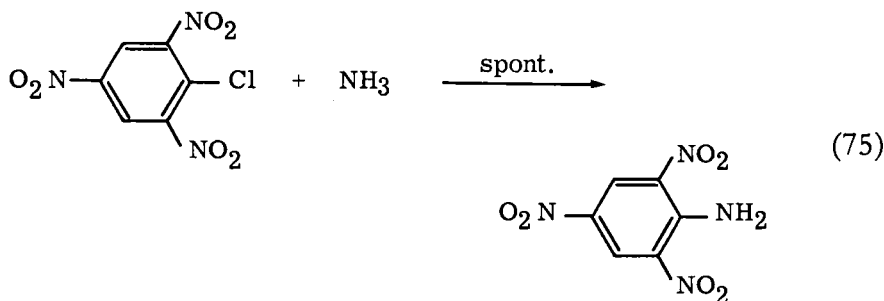
sulfide is that its action is sufficiently sensitive to steric hindrance that a free-standing nitro group can often be reduced while one next to an *ortho* substituent remains unaffected. A classical example of this effect

is that of 2,4-dinitrotoluene,⁸³ (Eq. 74); see Chapter 14. Lithium



aluminum hydride is not a satisfactory reagent for reducing aromatic nitro compounds to amines; reduction is incomplete.

The reaction of halides with ammonia,⁸⁴ which is important in aliphatic chemistry, has very limited use in the synthesis of aromatic amines. Most aryl halides are essentially inert to ammonia under convenient laboratory conditions, and only when strongly electron-withdrawing groups are *ortho* and *para* to the halogen (Eq. 75), as in 2,4-dinitrochloro-

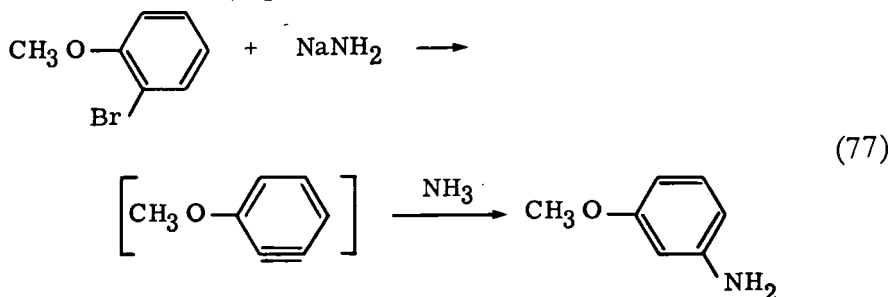


(commercial synthesis of aniline)

benzene, does reaction become easy.⁸⁵ With only one such activating group, reaction may still be possible with heating under pressure,⁸⁶ but most of the anilines obtainable in this way are more easily obtained by other methods. When there is no activating group, such as in chlorobenzene itself, aryl halides must be regarded as essentially inert toward ammonia. However, the reaction may still be forced under conditions feasible only in commercial installations, and this is the basis of the Dow aniline synthesis. Cuprous compounds are used as a catalyst, and the high temperatures required make high-pressure equipment necessary (Eq. 76).

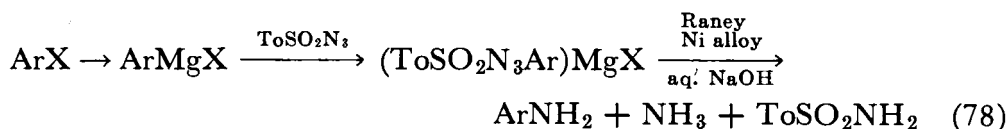
Conversion of aryl halides to amines may also be forced by use of metal amides, such as sodamide. In such cases, the amino group is not uncommonly found at a position other than the one occupied by the original halide, owing to the formation of a benzene intermediate, followed by addition of ammonia.⁸⁷ This type of rearrangement, sometimes called

ciné-substitution, can be of considerable advantage, such as in the preparation of *m*-anisidine⁸⁸ (Eq. 77), where neither the *m*-halo nor *m*-nitro



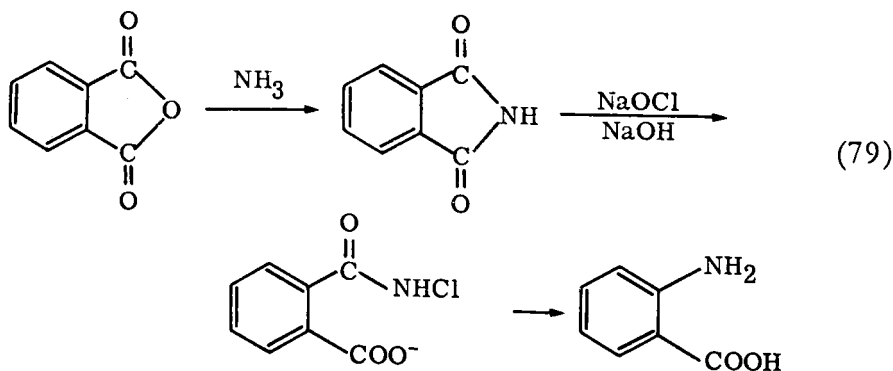
parent compound is readily available. It is in general to be expected whenever a very strongly basic reagent is used with an *ortho*-substituted aryl halide, as long as the reactivity toward direct displacement is low, owing to lack of activating substituents.

The aromatic halogen may also be converted to an amino group through the Grignard reagent,⁸⁹ which will react with toluenesulfonyl azide to form a triazene intermediate that can be reduced to an amine without isolation (Eq. 78). Alternatively, alkoxyamine or chloramine

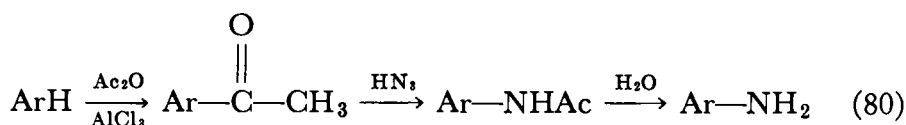


can be used with a Grignard reagent. These methods complement direct aminolysis, inasmuch as they are successful with (and are, in fact, confined to) aryl halides not bearing electron-withdrawing groups.

All of the rearrangement reactions of carboxyl derivatives that produce primary amines, as described in Chapter 2, are applicable to the synthesis of aromatic amines. These reactions are useful only in cases where the required acids are easily available, of course, and they only occasionally offer advantages over nitration and reduction. An important example of the commercial use of a rearrangement reaction is the synthesis of anthranilic acid from phthalic anhydride through phthalimide (Eq. 79).

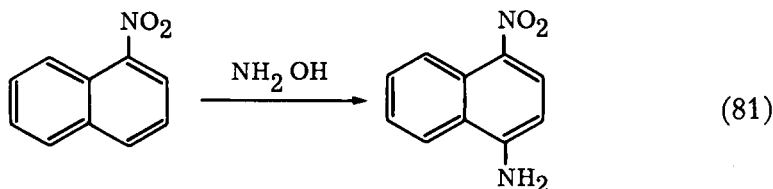


The conversion of ketones to amines, by either the Beckmann rearrangement of the oxime, or the Schmidt reaction with hydrogen azide, gives mostly aromatic amines when applied to aryl alkyl ketones such as acetophenones. Since such ketones can be prepared in great variety by Friedel-Crafts acetylation, the combination of steps is an efficient route to aromatic amines (Eq. 80), of value in situations where nitration is

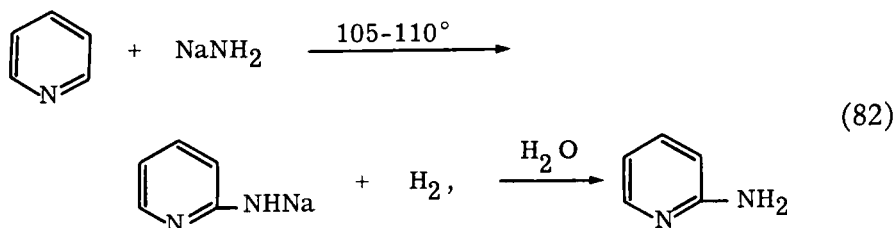


accompanied by difficulties, as in the case of phenanthrene.⁹⁰

Direct replacement of an aromatic hydrogen by the amino group is possible by several methods,⁸⁴ but the reactions are for the most part curiosities, with little preparative value. Hydroxylamine salts and certain derivatives, such as hydroxylamine-O-sulfonic acid, have been used with Friedel-Crafts catalysts,⁹¹ and hydrogen azide has been found to convert benzene to aniline under the influence of sulfuric acid, aluminum chloride, or ultraviolet light. Aromatic rings susceptible to nucleophilic attack, such as dinitrobenzenes and nitronaphthalenes, can be aminated *ortho* or *para* to the nitro groups by hydroxylamine in basic solution in useful yields⁹² (Eq. 81). The reaction of sodamide with pyridines, known as

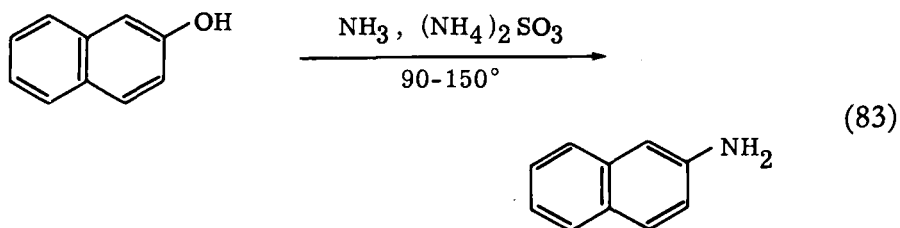


the Tschitschibabin reaction, is of commercial as well as laboratory use for the synthesis of α -aminopyridines⁹³ (Eq. 82).



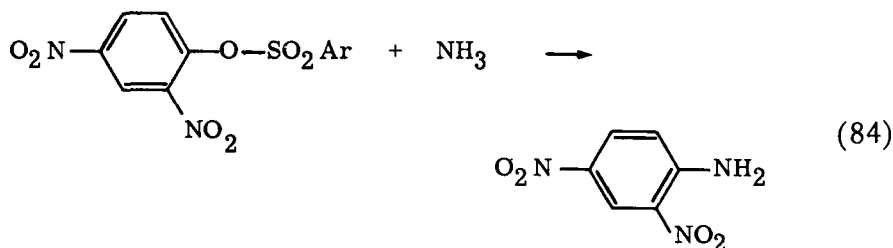
The phenolic hydroxyl group may be replaced by amino by means of the Bucherer reactions,⁵³ or by ammonolysis of a sulfonate ester. The Bucherer process is a valuable synthetic method for naphthylamines

(Eq. 83), but is almost useless with benzene derivatives. Aqueous

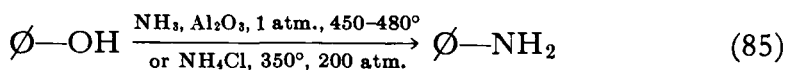


ammonia and ammonium sulfite is the reagent, and since the temperatures required, 90–180°, are well above the boiling point of the solutions, the reaction must generally be carried out in sealed tubes or autoclaves under pressure. The mechanism of the reaction, which is reversible, has been mentioned in connection with reactions of amines. The Bucherer reaction has important use in the preparation of naphthylamine derivatives, particularly in the dyestuff industries. Since 2-nitronaphthalene is not produced by direct nitration, but 2-naphthalenesulfonic acid can be obtained by sulfonation and then converted to 2-naphthol, the Bucherer reaction is the only practical source of 2-naphthylamine.

Ammonolysis of sulfonate esters of phenols is in general practical only in the presence of strongly activating substituents,⁹⁴ as in 2,4-dinitrophenols (Eq. 84), and is thus of quite limited use. Unactivated phenols



have been converted to amines industrially by treatment with ammonia or ammonium chloride at high temperatures and pressures⁹⁵ (Eq. 85),

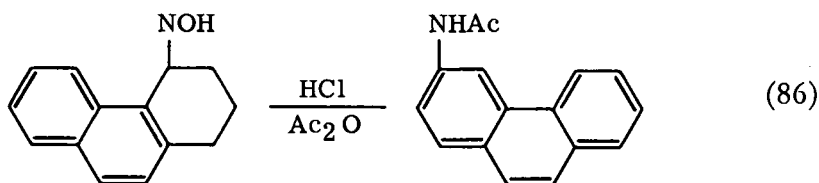


but such methods are seldom of laboratory use.

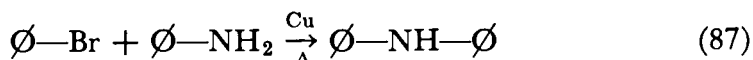
Aromatic primary amines can also be prepared from cyclic aliphatic amines by dehydrogenation,⁹⁶ best through their sturdier acetyl derivatives, but the reaction has seen little application. In certain cases, a kind of internal dehydrogenation can be carried out with cyclic oximes, the Semmler-Wolff aromatization⁹⁷ (Eq. 86) (Chapter 8), but the yields are seldom more than moderate.

Aromatic secondary amines are almost always prepared from aromatic primary amines, the principal exceptions being those cases where a reactive aryl halide, such as 2,4-dinitrofluorobenzene, can be used in

reaction with a primary aliphatic amine.⁸⁵ The Bucherer reaction can also be carried out so as to give secondary amines. The various synthetic methods for aliphatic secondary amines can in most instances be adapted to the preparation of aryl alkyl amines by obvious expedients; since these reactions are described in Chapter 2, more will not be said of them here.



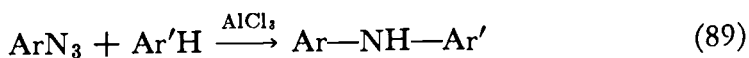
Diarylamines are a separate synthetic problem; they are for the most part made by arylation of a primary aromatic amine by special methods. Diphenylamine itself may be prepared by boiling aniline with its hydrochloride for many hours. Phenols have also been used as arylating agents in the presence of Lewis acids (such as anhydrous zinc chloride) with strong heat, but the method is not much used. Naphthols, however, give diarylamines readily by the Bucherer reaction. The most useful preparative method uses aryl halides, even "unreactive" ones, such as bromobenzene, to arylate aromatic amines^{106, 98}; finely divided copper ("copper bronze") or cuprous halide catalysts enable the reaction to be carried out at or below the boiling points of the reactants (thus at about 200°) (Eq. 87), and pressure vessels are not required. The method is sometimes



called the Ullmann reaction, but this term is likely to be confusing, since it is more commonly used for the preparation of biaryls from aryl halides and copper. When electron-withdrawing groups *ortho* or *para* to the halogen provide activation, arylation proceeds more readily, of course.⁸⁴ Arylation of aromatic amines as their anions, in the form of sodium anilide, for example, is much easier, and can be accomplished with all types of aryl halides^{13, 84, 98c,d} (Eq. 88).

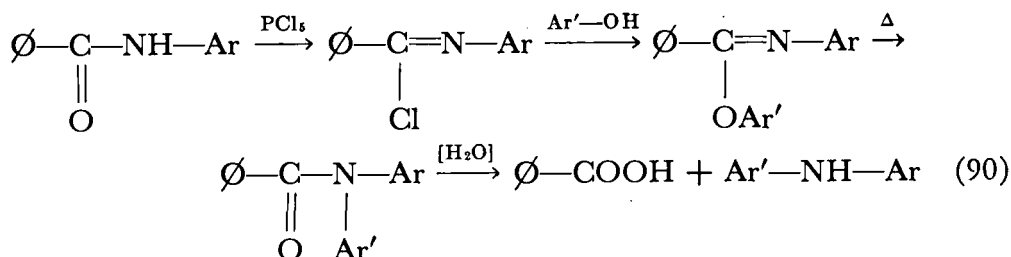


The anilino group can be introduced directly into an aromatic hydrocarbon by use of aryl azides and aluminum chloride; yields are less than 50%, however⁹⁹ (Eq. 89).



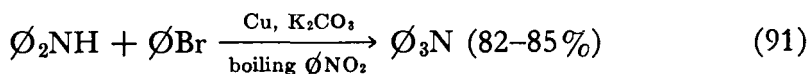
Diarylamines can also be prepared by the Chapman rearrangement¹⁰⁰

(Eq. 90); electron-withdrawing substituents on the aryl group that must



migrate from oxygen to nitrogen facilitate the reaction (see Chapter 4). The required imidoyl esters are easily prepared by treating the benzoyl derivative of an aromatic primary amine first with phosphorus pentachloride and then with a phenol.

Triarylamines are prepared by arylation of diarylamines ⁹⁸ (Eq. 91).



DIAMINES, POLYAMINES, AND QUINONE IMINES

The influence of most ring substituents on the chemical properties of aromatic amines is only quantitative; the characteristic reactions usually remain unchanged. Hydroxyl and additional amino substituents may cause qualitative changes in the chemistry, however, when they are *ortho* or *para* to the amino group; for this reason, these compounds are discussed separately in this section.

The three diaminobenzenes are easily prepared by ordinary reactions; they are colorless solids that are rather sensitive to air oxidation, and as usually obtained are discolored. The presence of two hydrophilic groups on one benzene ring would be expected to increase water solubility considerably over aniline, but, as with the aminophenols, does so only in the case of the *meta* isomer. Both amino groups are basic enough to form salts with aqueous acids; *p*-phenylenediamine is more than ten times as strong as its isomers (see Table 3-3).

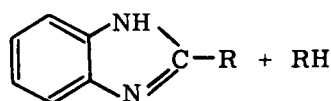
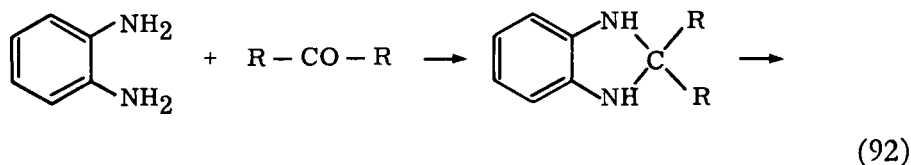
***m*-PHENYLENEDIAMINE** *m*-Diaminobenzene (*m*-phenylenediamine) shows the ordinary chemical behavior of monoamines, and there is nothing exceptional about it. Both amino groups can be diazotized, but very strong acid is required to prevent self-coupling.¹⁰¹ In more weakly acidic solutions, self-coupling occurs to give a *bis*-azo dye called Bismarck brown, of value as a stain and as a reagent for the colorimetric estimation for nitrous acid.¹⁰²

Table 3-3 *Properties of some aromatic diamines and amino phenols*

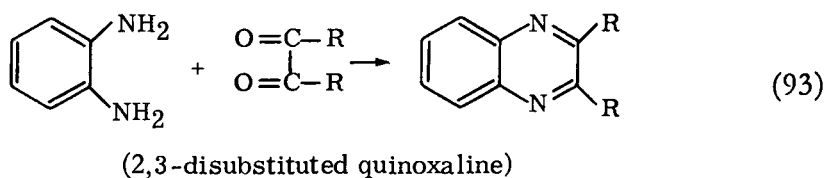
Amine	pK _a of H ₂ NArNH ₃ ⁺	K _b × 10 ¹⁰	pK _a of Ar(NH ₃ ⁺) ₂	mp	bp
<i>o</i> -Phenylenediamine	4.47	3.0	1.3	104°	252°
<i>m</i> -Phenylenediamine	4.88	7.6	2.65	63°	287°
<i>p</i> -Phenylenediamine	6.08	120	3.29	142°	267°
Benzidine	4.89	7.8	3.74	128°	401°
<i>o</i> -Aminophenol	4.72	5.2		174°	subl.
<i>m</i> -Aminophenol	4.17	1.5		122°	164°/11 mm
<i>p</i> -Aminophenol	5.50	32		186°	subl.

(Dissociation constants taken from R. Kuhn and A. Wassermann, *Helv. Chim. Acta*, **11**, 3 (1928), and R. Kuhn and F. Zumstein, *Ber.*, **59**, 488 (1926).)

***o*-PHENYLENEDIAMINE** The chemistry of *ortho*-phenylenediamine is dominated by ring-closure reactions. A molecule of aldehyde or ketone reacts with both amino groups, producing benzimidazolines. These substances have the remarkable property of expelling hydrogen or a hydrocarbon on heating, forming benzimidazoles,¹⁰³ in which the five-membered ring has also become aromatic (Eq. 92). *Ortho*-mercapto



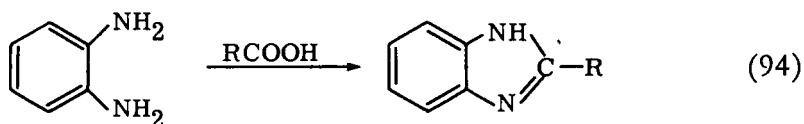
anilines show parallel behavior. α -Diketones react in a special manner, forming the fully aromatic ring system quinoxaline¹⁰⁴ (Eq. 93). The



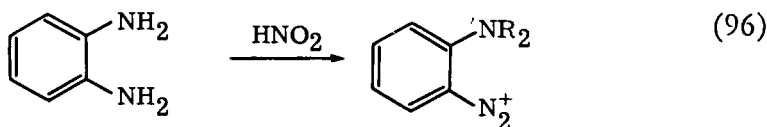
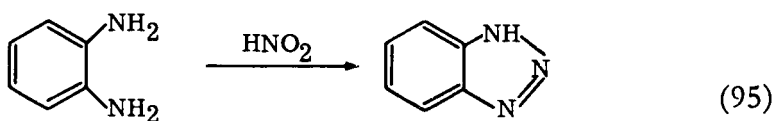
reaction occurs so readily, and the sparingly soluble products are so easy to isolate, that the reaction is a valuable diagnostic method for the α -diketone structure.

Acylation of *o*-phenylenediamines may give either mono- or di-acyl derivatives, but both types cyclize very easily to form benzimidazoles.

This reaction occurs so readily that benzimidazoles can be formed by heating *o*-phenylenediamines with amides, esters, or even free acids ¹⁰⁵ (Eq. 94); only when milder conditions can be used, such as with the use

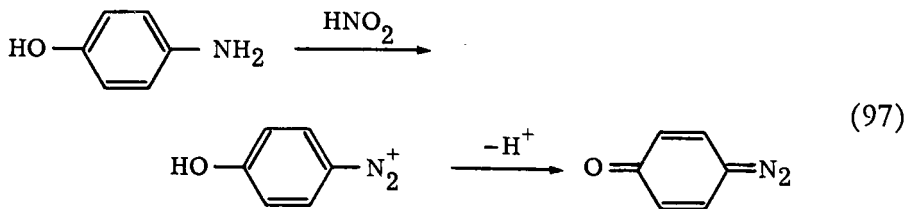


of acid anhydrides or chlorides under Schotten-Baumann conditions, are normal amides obtained.¹⁰⁶ Nitrosation proceeds parallel to other types of acylation; instead of diazonium compounds, benzotriazoles, isoelectronic with benzimidazoles, are ordinarily formed ¹⁰⁷ (Eq. 95). This type of reaction clearly requires that one amino group be primary, and the other primary or secondary; when one amino group is tertiary, as in *o*-dimethylaminoaniline, a normal diazonium salt can be produced (Eq. 96). *Bis*-diazonium salts of *o*-phenylenediamines can be formed by



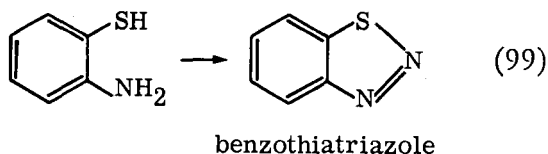
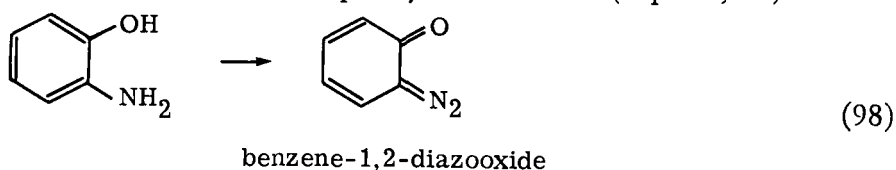
use of nitrosylsulfuric acid in glacial acetic acid, owing to the suppression of coupling by the strong acidity.¹⁰⁸ *p*-Phenylenediamines cannot cyclize, of course, and can therefore be diazotized to a *bis*-diazonium salt more readily,¹⁰⁸ like the *meta* isomer.

HYDROXY ANILINES All three hydroxy anilines react with nitrous acid to form diazonium salts. That of the *meta* isomer is normal, but the *ortho* and *para* isomers become diazo-oxides when the acidity is reduced (similar behavior is shown by the mercapto anilines) (Eq. 97). The *para*

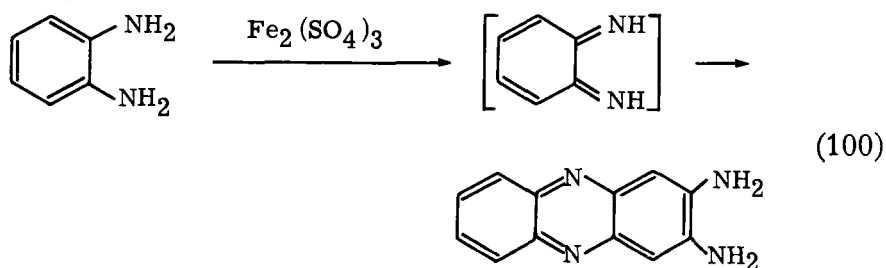


isomers are of necessity quinone derivatives,¹⁰⁹ but the *ortho* isomers present a more difficult problem. The best evidence indicates that *ortho*-hydroxy anilines form true diazo-oxides rather than benzoxadiazoles, but *ortho*-

mercapto anilines give rise to benzothiadiazoles, analogous to the formation of benzotriazoles from *o*-phenylenediamines (Eqs. 98, 99).



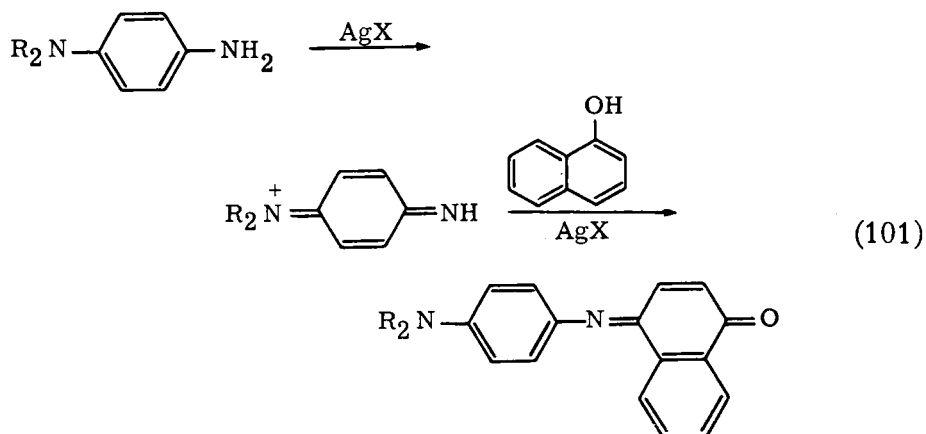
OXIDATION It is in their oxidation reactions that the *ortho* and *para* diamines and hydroxy amines show the most striking differences from the monoamines. *o*-Phenylenediamine turns deep red with oxidizing agents ¹¹⁰; ferric sulfate in aqueous acid is particularly effective. A kind of double coupling results in the formation of the phenazine ring system; it seems probable that *ortho*-quinone diimine is an intermediate ¹¹¹ (Eq. 100).



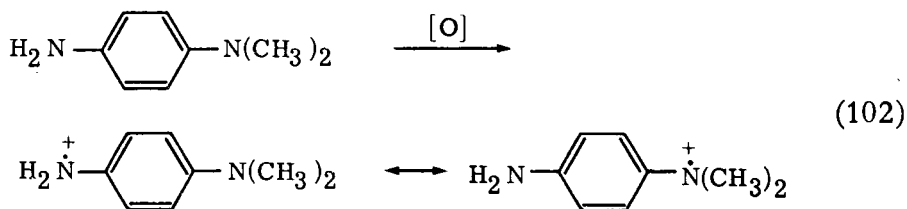
p-Phenylenediamine is converted by careful oxidation into colorless *p*-quinone diimine,¹¹² and *p*-hydroxyaniline into quinone monimine, a pale yellow solid. An intermediate cation-radical oxidation stage can be identified; that from diaminodurene, for example, has been shown to be monomeric, paramagnetic, and to give an electron-paramagnetic-resonance signal.¹¹³

The presence of aryl, alkyl, or acyl substituents on the amino nitrogen does not interfere with oxidation, and a great variety of derivatives can be made in this way.¹¹⁴ The resulting quinonimines are very reactive, and undergo numerous addition reactions at the C—C double bond, like quinones. They are easily hydrolyzed to quinones, and are sometimes intermediates in their synthesis.¹¹⁵ They can be reduced back to phenylenediamines by sulfur dioxide or dithionite, but are in general unstable to storage, and easily condense to deeply colored substances. Their chemistry is of importance in the field of color photography; the dyes are commonly produced by oxidative condensation of a *p*-phenylene-

diamine with a "coupler," such as α -naphthol, to produce an indaniline dye ¹¹⁶ (Eq. 101).



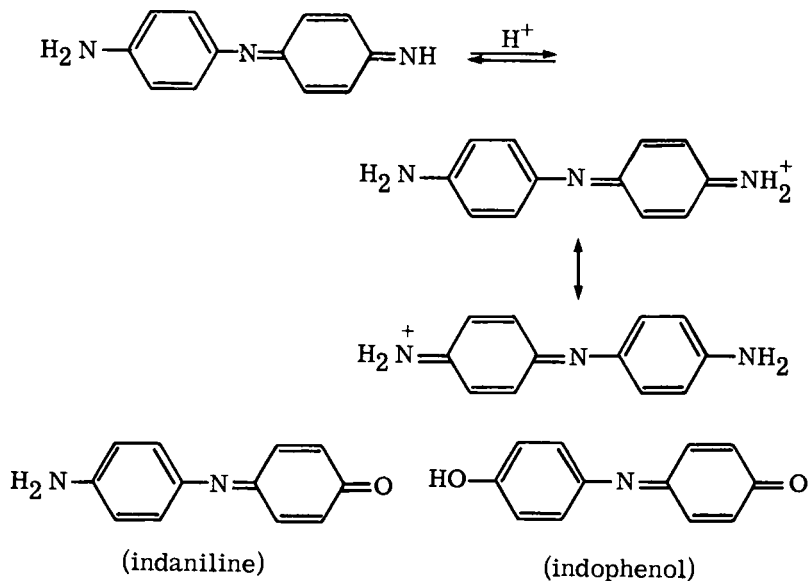
p-Phenylenediamines having two substituents on one nitrogen cannot, of course, form an uncharged quinone diimine; they are nevertheless oxidizable in acid solution, a ternary immonium ion being formed, as illustrated in Eq. 101. In base-catalyzed hydrolysis, the substituted nitrogen is preferentially removed first, producing quinone monimines. Although quinone diimines are colorless or nearly so, the oxidation reactions that produce them are usually accompanied by intense colors. The species responsible for the color are cation-radicals, representing an oxidation stage halfway between the diamine and the quinone diimine structures ¹¹⁷ (Eq. 102). As a class, they are referred to as semiquinones,



and have been the object of intense interest. The pioneer investigator in this field was C. Würster, and the semiquinones are therefore often called "Würster's salts." They are reversibly oxidizable or reducible to the extreme oxidation states. They were at one time thought to be analogous to quinhydrone, which is not a free radical, but a hydrogen-bonded polymer of quinone and hydroquinone, considerably dissociated into its components in solution.

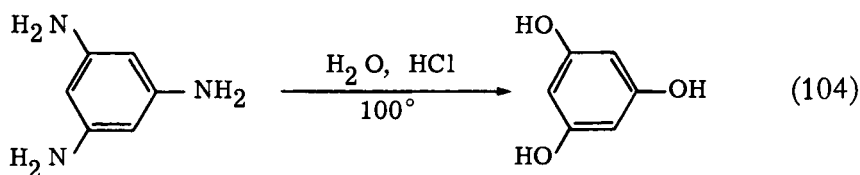
Similar behavior of a more extensive form is shown by *p*-phenylenediamines and *p*-hydroxyanilines that bear a *p*-aminophenyl or *p*-hydroxyphenyl group on an amino group. In such cases, the quinone imine derivatives resulting from oxidation are capable of tautomerism, or, when

protonated, have a delocalization of the ionic charge over both aromatic rings (Eq. 103). They are often intensely colored, and have received



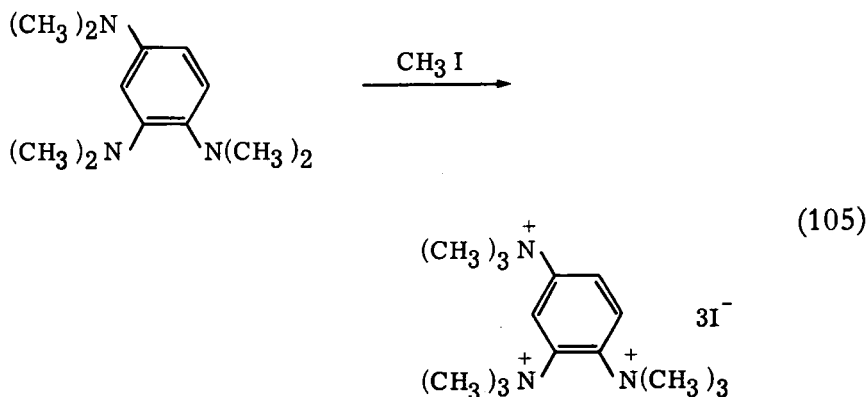
much attention from the dyestuff industries and in connection with the theory of color and constitution. The three possible types have special class names, as shown. These substances may also be formed by other reactions, such as the oxidation of anilines, coupling reactions of quinone N-chloroimines,¹¹⁸ and Liebermann's nitroso test (see Chapter 13), and in the oxidative coupling of *p*-phenylenediamines in the color-development phase of color photography.¹¹⁵

POLYAMINO BENZENES All the polyamino benzenes are known up to hexaminobenzene.¹¹⁹ All are solids, distinctly basic, but they do not appear to form salts with more than three moles of acid, and usually not more than two. In general, their chemistry does not show features not already exemplified by the diamines, except for pronounced ease of hydrolysis. Phloroglucinol (1,3,5-trihydroxybenzene) is conveniently prepared by boiling 1,3,5-triaminobenzene hydrochloride in water (Eq. 104), for example¹²⁰ (the amine itself is obtained by the reduction of



1,3,5-trinitrobenzene). Hexaminobenzene, mp 247–248°, is somewhat less reactive than the other polyamino benzenes.

Of all the polyamino benzenes with two adjacent amino groups, only one, 1,2,4-triaminobenzene, has been reported to give rise to a completely quaternized derivative¹²¹ (Eq. 105). In addition to the steric crowding resulting from adjacent trimethylammonio groups, which are

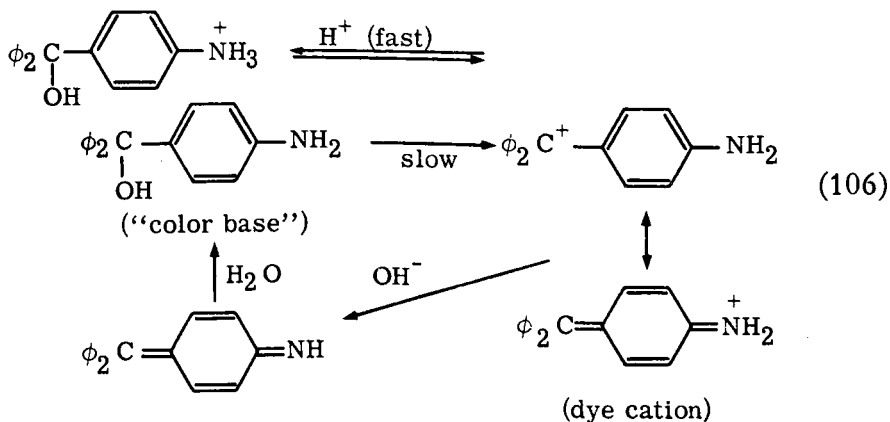


homomorphic (having the same number of nuclei in the same geometry) with *tert*-butyl, there is the repulsion of like charges. It is not surprising, therefore, that the *tris*-methiodide of 1,2,4-*tris*-(dimethylamino)benzene readily loses a molecule of methyl iodide.

AMINOTRIARYLMETHANE DYES

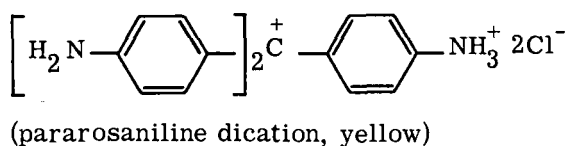
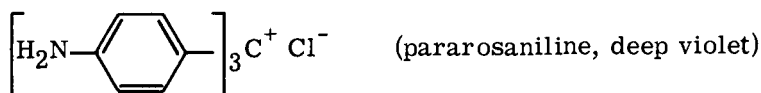
The triphenylmethane dyes have been the object of an enormous amount of scientific and technical attention, beginning with the accidental synthesis of fuchsine (rosaniline) in 1859. By no means all of them are aromatic amines, but many of the important ones are, and it is appropriate to call attention to their special chemistry here.

Triphenylmethanes and their amino derivatives¹²² are not especially different from simpler compounds of the same type, except for the ease with which they are oxidized to triphenylcarbinols. When suitably substituted, particularly with amino groups in one or more *para* positions, triphenylcarbinols generally form salts of extremely intense color when treated with acids; the colored substances are not formed by simple addition of a proton, but by actual loss of water. The carbinols are thus pseudo bases. The process is well illustrated by *p*-aminotriphenylcarbinol¹²³ (Eq. 106). It forms a conventional ammonium ion



immediately upon treatment with acid; this ion then loses water at an observable rate to form the colored anhydro ion, whose structure can be represented as a triarylcarbonium ion or as a quinone imine derivative. Careful treatment with base liberates the free quinone imine (fuchsone imine), which only slowly takes up water to re-form the original carbinol, or other nucleophiles to form triarylmethyl ethers, cyanides, amines, etc.¹²⁴ A competing reaction is hydrolysis of the imino moiety to a carbonyl group, forming a fuchsone.¹²⁵

The color of the anhydro ions becomes more intense and moves toward the blue end of the spectrum as the remaining *para* positions are successively provided with amino groups. This effect disappears, however, when an amino group is quaternized, when it is acylated, or when it is converted to an ammonium ion by excess acid.¹²⁶ Such behavior strongly suggests that the colored ions have a highly delocalized electronic structure, in which the unshared electron pairs of the amino groups are involved, and whose limiting states can be represented by quinoid struc-



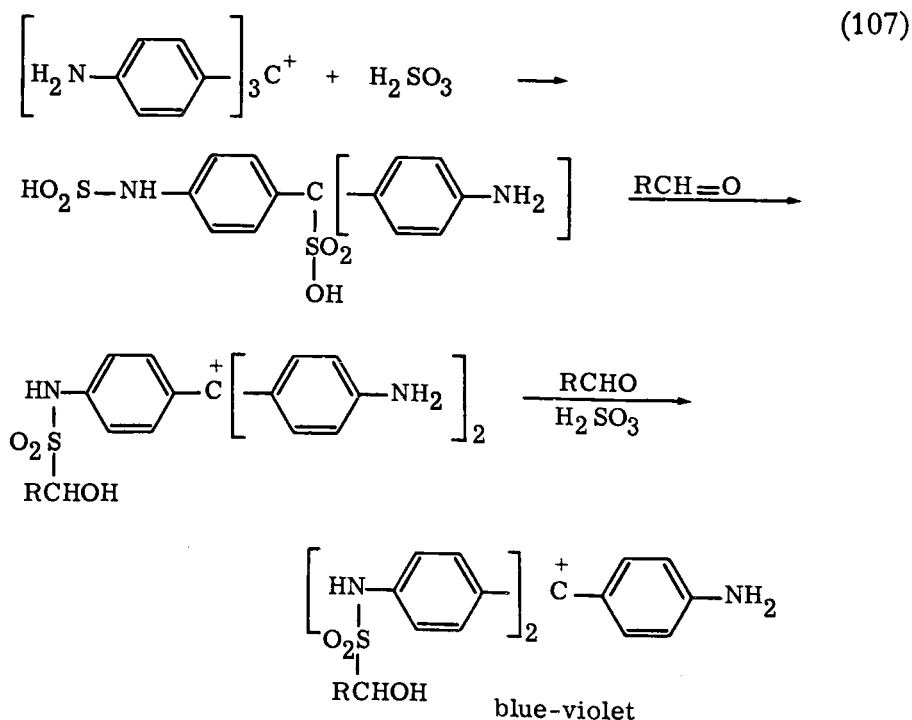
tures, of the type shown in Eq. 106 for the monoamino member of the group.

The structure of the triphenylmethane dyes remains somewhat ambiguous, however. A completely delocalized electronic structure for pararosaniline, for example, would require a completely coplanar ion, but in such an arrangement, there would be serious interference between the *ortho* hydrogens of the aryl groups. Presumably, then, at least two of the benzene rings must be rotated somewhat out of the plane, which would correspondingly reduce the extent of π -orbital overlap. Nuclear magnetic resonance spectra indicate that the triphenylcarbonium ion, $\text{C}_6\text{H}_5\text{C}^+(\text{C}_6\text{H}_5)_2$, and some of its substituted derivatives have equivalent phenyl groups, which implies a propeller-shaped ion.¹²⁷ There is also abundant information on the electronic spectra of triarylmethane dyes.¹²⁸

The colorless triarylcarbinols are known as "color bases" or "carbinol bases," and the triarylmethanes from which they are so easily obtainable by oxidation are known as "leuco bases." The amino groups in all these compounds, including the dyes, show the normal reactions of amines of their class, such as acylation, diazotization, etc.

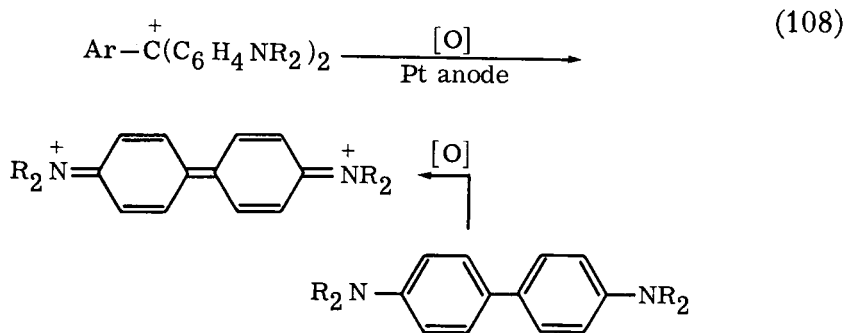
Crystal violet and methyl violet, widely encountered representative triarylmethane dyes, are hexamethyl and pentamethyl N-substituted pararosaniline, respectively. Malachite green, with two amino groups, both fully methylated, has been mentioned earlier in this chapter, in connection with the general method of preparation by condensation of aldehydes or ketones with aromatic amines. A variant of this synthesis is the oxidation of a suitably substituted toluene derivative in the presence of an aromatic amine. This was the method by which Verguin prepared the first known example, and presumably involves the formation of a benzaldehyde *in situ*. The technical importance of the triphenylmethane dyes has dropped considerably since the nineteenth century, for although they are bright and intense in color, they often have poor stability, especially toward light.

A reaction of special interest is the Schiff test for aldehydes, in which a purple color is generated by reaction with a solution of pararosaniline that has been bleached with sulfur dioxide.¹²⁹ The colorless solution is believed to contain a number of species in equilibrium, among which is an N-sulfinic acid derivative of a triarylmethanesulfonic acid, which loses the C-sulfo group as HSO_3^- after the aldehyde has reacted with the sulfinic acid groups. A new triarylcarbonium ion is thereby generated, whose color differs slightly from that of the parent pararosaniline (Eq. 107).



Triarylmethane dyes are generally the end products of oxidation, and

thus not very susceptible to further oxidation. However, a curious degradation has been observed by both chemical and electrolytic oxidation.¹³⁰ Crystal violet and some related dyes lose one aryl group and the aliphatic carbon to become diphenoquinonimine salts, which are more simply related to benzidines, of which they are the normal oxidation products¹³¹ (Eq. 108).



Much of the chemistry of the aminotriarylmethane dyes finds a parallel in the behavior of Michler's hydrol,¹³² *p,p'*-tetramethyldiaminobenzhydrol, which also forms intensely colored salts, but does not have dye properties.

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chapter four

Amides

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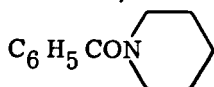
CARBOXYL DERIVATIVES

A. Carboxamides

NOMENCLATURE Amides are almost invariably named by replacing the “-ic” ending of the name of an acid with the suffix “-amide.” This is equally true whether the acid name used is primitive, as in “valeramide,” or systematic, as in “pentanoamide.” Occasionally the letter “o” is also dropped from acid names ending “-oic,” and occasionally “-onic” as a whole is replaced by “-amide,” as in “carbamide” (urea).

Substituents on the nitrogen atom of amides are designated by the locant “N-,” as in “N-methylacetamide”; in the older literature this locant was sometimes replaced by a reversed word order, as in “acetmethylamide.” In cases where no confusion is likely, the locants may be omitted because they are obviously implied, as in “dimethylformamide” ($\text{HCON}(\text{CH}_3)_2$). N-Aryl amides are usually named with the suffix “-anilide” or appropriate analogue in place of the terminal “-ic” of the

acid name, as in "benzo-*p*-toluidide," $\text{C}_6\text{H}_5\text{—CO—NH—C}_6\text{H}_4\text{—p—CH}_3$, and "acetanilide," $\text{CH}_3\text{CO—NH—C}_6\text{H}_5$. This system is also of occasional convenience with heterocyclic bases, as in "benzopiperidide."



In the occasional case where it is necessary to express the presence of an amido group as a prefix, the method to be used depends on whether the attachment to the root-name structure is through the nitrogen or the carbonyl carbon. In the former case, the form "-amido-" is used, as in "*tris*(acetamido)methane," $(\text{CH}_3\text{CONH})_3\text{CH}$. When attachment is through carbonyl, "carbamoyl" (formerly "carbamyl"), derived from carbamic acid, is the prefix, as in "4-(dimethylcarbamoyl)crotonic acid," $(\text{CH}_3)_2\text{NCO—CH}_2\text{—CH=CH—COOH}$.

PROPERTIES The physical properties of amides are greatly influenced by the strong hydrogen-bonded association encountered in them. Just as with carboxylic acid, they are considerably dimerized in nonpolar solvents. The boiling points of unsubstituted amides lie approximately 100° higher than those of the corresponding acids, a combined result of hydrogen bonding and a high dipole moment (over 3 D). Melting points are also higher, and formamide is the only unsubstituted straight-chain aliphatic amide that is liquid at room temperature. Substitution on the nitrogen interferes with the association, and may actually lower the boiling point if the substituent is small, such as methyl. The melting point is also lowered, and many dimethylamides are liquids at room temperature. Some selected values of physical properties are presented in Table 4-1.

The amido group has a pronounced affinity for water, and formamide is completely miscible, and acetamide is extremely soluble, so much so that it is hygroscopic. Valeramide, with five carbons, is still water-soluble, but with one carbon more, caproamide is generally classified as insoluble. The solubility of amides in ether and other nonpolar solvents is low when the amido group constitutes an appreciable percentage of the molecule. Actually, amides themselves are good solvents;

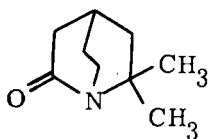
Table 4-1 *Properties of some amides*

HCONH_2	CH_3CONH_2	$\text{CH}_3(\text{CH}_2)_4\text{CONH}_2$	HCONHCH_3
Bp 210° dec.	222°	255°	185°
Mp 2.5°	81°	101°	liq.
pK _a -0.5	0.1	-0.05	-0.04
$\text{HCON}(\text{CH}_3)_2$	$\text{CH}_3\text{CONHCH}_3$	$\text{CH}_3\text{CON}(\text{CH}_3)_2$	$\text{C}_6\text{H}_5\text{CONH}_2$
Bp 155°	206°	166°	290°
Mp $< -55^\circ$	28°	liq.	130°
pK _a -0.01	0.8		-1.85

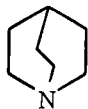
they have exceptionally high dielectric constants (109 for formamide, 200 at 15° for N-methylformamide, 38 at 15° for dimethylformamide, 165.5 at 40° for N-methylacetamide, 65 for acetamide), and dissolve many inorganic salts to give highly conducting solutions.¹ Liquid amides, particularly dimethylformamide, have assumed great importance as reaction solvents since 1945, owing to the great reactivity of anions in such media.

The acid-base properties of amides reflect the acid-strengthening, base-weakening influence of the acyl group. The effect of the substitution of an acetyl group on water, giving acetic acid, is to increase the acid strength and decrease the basic strength by factors of roughly 10^{10} . The same effect appears in amides, and K_b of acetamide has been reported to be 3×10^{-15} (cf. K_b for ammonia, 1.8×10^{-5}), and K_a , 8.3×10^{-16} ; further values are given in Table 4-1.² It can be seen that the basicity of amides is very close to that of water, that N-alkylation increases the basic strength slightly and that aryl substitution has the reverse effect. Acetanilide,^{2e} for example, is a weaker base than acetamide by a little more than one power of 10. The acidity of amides varies with structure in the same way as that of carboxylic acids; nearly all of them are weaker acids than water, and roughly similar to alcohols.³ As would be expected, an N-alkyl group decreases acidity, and an N-aryl group increases it.

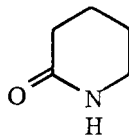
The acid-base properties of the amido group are apparently greatly influenced by the delocalization of π -electrons in the O—C—N system, and the properties are properly considered as belonging to the group as a whole, not to the nitrogen atom. This is borne out by the fact that protonation of the amido group⁴ occurs on oxygen, not nitrogen, which would be expected to acquire the proton in the absence of electron delocalization, and thus gives the ion $[R-C(OH)NH_2]^+$. Benzamide, for example, shows an ultraviolet spectrum in concentrated sulfuric acid that is essentially superimposable on that of the related imidate ester, $\phi-C(OEt)=NH_2^+$. π -Orbital overlap between carbon and nitrogen is prevented by steric effects in 2,2-dimethylquinuclidone-6, owing to the inability of the system to rotate about the C—N bond into the proper position. As a consequence, the basicity is increased enormously,^{4d} and significantly, protonation is believed to occur on nitrogen. Since this bicyclic amide is still a weaker base by five powers of 10 than quinuclidine, a tertiary amine having a similar carbon skeleton, it is evident that the carbonyl group also has a strong base-weakening inductive effect. The situation is in many ways analogous to the effect of structure on the basicity of arylamines (see Chapter 3).



2,2-dimethyl-
quinuclidone-6
 $pK_a = 5.33$



quinuclidine
 $pK_a = 10.8$



α -piperidone
 $pK_a = 0.8$

The structure of unsubstituted and monosubstituted amides has been a topic of discussion for many decades, and appears to have been resolved relatively recently by the application of physical methods, such as microwave spectroscopy and nuclear magnetic resonance. The conventional

structure, $\text{O}=\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{NH}_2$, and not the enol tautomer, $\text{HO}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}=\text{NH}$, has been found to be generally correct. However, even in N,N-disubstituted amides there is significant π -orbital overlap in the OCN system, which restricts rotation about the C—N bond and leads to a planar molecule.^{5a} The infrared spectrum of primary and secondary amides is characterized by a doublet in the double-bond stretching region (1630–1680 cm^{-1} , 1515–1650 cm^{-1}), and amide carbonyl groups can usually be distinguished readily from ester and carboxyl carbonyls. The carbonyl stretching frequency of tertiary amides, RCONR_2 , is usually found at 1630–1670

cm^{-1} , but in quaternary amides,^{4a} RCONR_3^+ , this frequency is raised to near 1800 cm^{-1} , owing to the strong electron withdrawal.

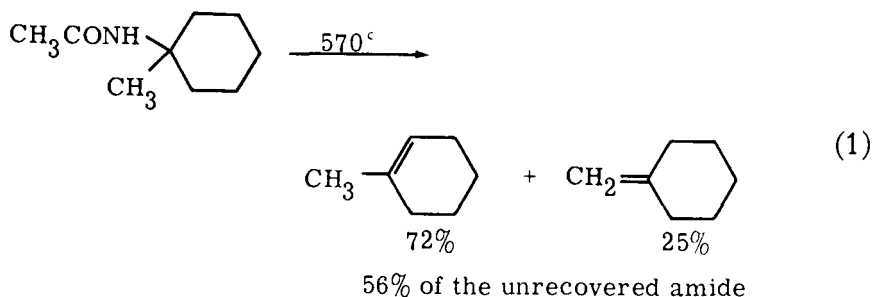
Like carboxylic acids, unsubstituted amides form hydrogen-bonded dimers extensively in solution.^{5b}

OCCURRENCE AND USE Some simple amides occur in nature, urea, the amide of carbonic acid, being the commonest. A number of N-substituted amides belong to the alkaloid group, and are important although not widespread. Piperine is a simple example; it is the piperidide of piperic acid, and is responsible for part of the taste of pepper. Colchicine, an alkaloid of medicinal importance obtained from the autumn crocus, is a more complex example. Polyamides are widespread and of fundamental importance in both the plant and animal worlds, for proteins and peptides contain long chains of amide linkages.

Industrial use of amides was rather limited until recent years. Urea has long enjoyed commercial application, as in the urea-formaldehyde resins (Chapter 6). The development of the nylon polyamide fibers took place in the 1930's. The two commonest are nylon 66, which is derived from adipic acid and hexamethylenediamine, and has the repeating unit $-\text{NH}-\text{CO}(\text{CH}_2)_4\text{CO}-\text{NH}-(\text{CH}_2)_6-$, and nylon 6, derived from ϵ -aminocaproic acid, having the repeating unit $-\text{NH}-(\text{CH}_2)_5-\text{CO}-$. Some low-melting amides, such as dimethylformamide, have become valuable industrial as well as laboratory solvents.

REACTIONS *Heat* Amides are in general very stable substances, and even high-boiling ones can usually be distilled with little decomposition. At temperatures above 500°, however, N-alkyl amides eliminate the alkyl group as olefin, in a reaction that is surprisingly clean considering the conditions required⁶ (Eq. 1). The reaction in all probability passes through a cyclic transition state, resulting in *cis* elimination. The Hof-

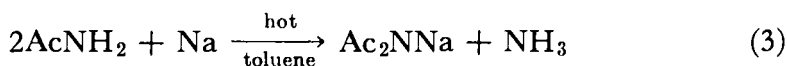
mann rule is only partly followed, however, and mixtures of isomeric olefins are obtained.



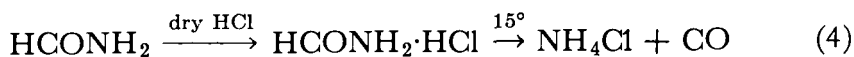
Salt formation Amides can form salts with both acids and bases, but both classes of salts are in general readily hydrolyzed by cold water. Some amides can nevertheless form salts stable in the presence of water, especially if the salt is of low solubility or is not highly polar. Sodium amide or hydride in the absence of water converts simple amides to ionic sodium salts (Eq. 2); mercuric oxide, on the other hand, gives derivatives



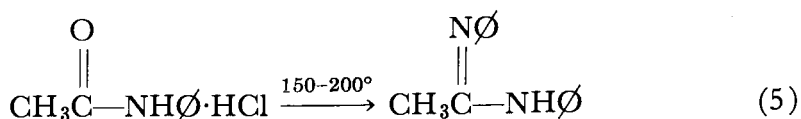
resistant to hydrolysis. The direct reaction of amides with sodium or potassium is not a satisfactory way to prepare amide salts, however. Although a reaction occurs, it can only take place on the metal surface, and is therefore slow. There is thus time for the amide salt to react with more amide, producing ammonia and the salt of the imide (Eq. 3). In



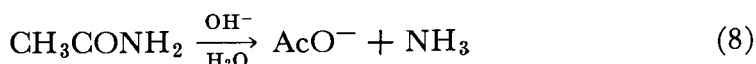
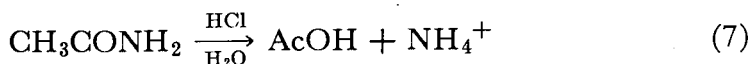
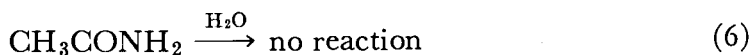
strong mineral acid solution, such as concentrated hydrochloric acid, most amides are converted largely to cations, RCOHNR_2^+ , but the corresponding crystalline salts can usually be isolated only in the absence of water (in 1 to 4N hydrochloric acid, amide salts would be about half hydrolyzed to free amide). Some amide trichloroacetates can be precipitated from water solution, however. Formamide hydrochloride is formed from hydrogen chloride dissolved in ether; it is unusual in that it decomposes explosively at 15° into ammonium chloride and carbon monoxide (Eq. 4). In contrast, acetamide hydrobromide, formed simi-



larly, can be sublimed at $95\text{--}100^\circ$. Acetanilide hydrochloride is stable enough to resist decomposition until about 150° , above which it disproportionates to give N,N'-diphenylacetamidine ⁷ (Eq. 5).

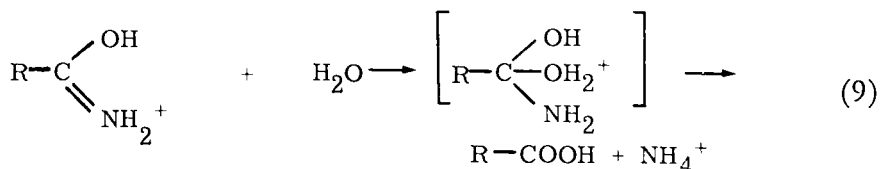


Hydrolysis The hydrolysis of amides (Eqs. 6–8) is a seemingly simple



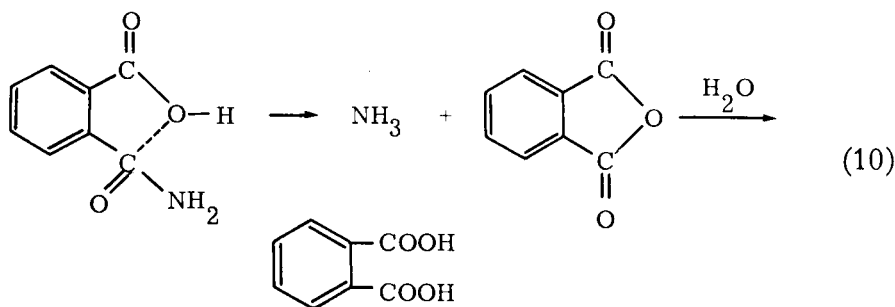
subject, but actually it has many ramifications. Water alone is essentially inert toward most of them, and boiling water is often an excellent solvent for their recrystallization, although quaternary amide salts, $\text{RCONR}_3^+\text{X}^-$, are immediately hydrolyzed by cold water. Hydrolysis is catalyzed by both acids and bases,⁸ but even then is apt to be slow. Hydrolysis is appreciably slowed down by branching in the neighborhood of the amido group, as a result of interference with the approach of H_2O (or OH^-) to the carbonyl carbon, and highly hindered amides may become virtually unhydrolyzable. Although dilute hydrochloric acid at room temperature will hydrolyze acetamide at a reasonable rate, 1-phenanthranilide is hydrolyzed only by heating with concentrated hydrochloric acid and acetic acid in a sealed tube at 200° . Hot, sirupy (80%) orthophosphoric acid is also a useful reagent for otherwise resistant amides.

The hydrolysis of amides in acid solution is apparently a bimolecular process involving attack of a water molecule on the protonated amide (Eq. 9). The catalytic influence is accordingly not directly proportional



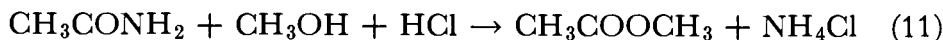
to the concentration of acid, but reaches a maximum at acidities where the amido group is largely converted to the protonated form (roughly about 6 *M* hydrochloric acid), after which further increase of acidity simply reduces the availability of water molecules.^{9, 10} Base catalysis, of course, involves attack of OH^- on the carbonyl group. Functional groups within the same molecule may be able to furnish the required proton to the amino group and at the same time a nucleophilic oxygen to the carbonyl carbon.⁹ Indeed, with a compound such as phthalamic

acid (Eq. 10), the neutral molecule may hydrolyze much faster than does



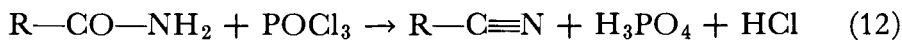
the protonated form of simple amides. Enzymatic hydrolysis of amides, of enormous importance in the biochemistry of peptides and proteins, probably involves a similar concerted action.¹¹

Amides may also be solvolyzed by agents other than water. With alcohols, for example, esters are produced when acid catalysts are used (Eq. 11). Primary amines, and particularly hydrazine, in many cases

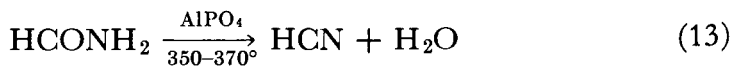


react with amides fairly readily on heating, even without additional catalyst. Such reactions usually proceed in the direction that expels the more volatile amine when it is possible for one to escape.

Dehydration Phosphorus pentoxide is the classical reagent for dehydrating unsubstituted amides to nitriles,¹² but it is inconvenient to work with. Acid chlorides of the mineral acids are also generally effective, and phosphorus pentachloride, phosphoryl chloride (POCl_3), and thionyl chloride (SOCl_2) are all of preparative value (Eq. 12). They

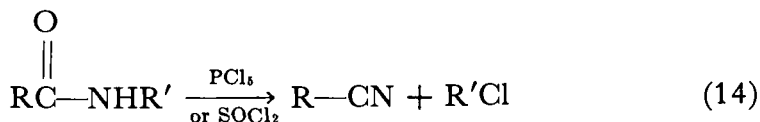


appear to form initial addition complexes that decompose to nitriles on heating. Even organic acid chlorides, such as phosgene and 3,5-dinitrobenzoyl chloride, can be used. Acetic anhydride will dehydrate acetamide to acetonitrile, but the reaction is incomplete, equilibrium being reached at 83% conversion for equimolar mixtures at 98°. Catalytic dehydration is also possible, and has valuable industrial application, such as in the production of hydrogen cyanide from formamide. A wide variety of contact catalysts, such as alumina, pumice, or thoria, have been used, and the temperatures are invariably high (200–500°) (Eq. 13).



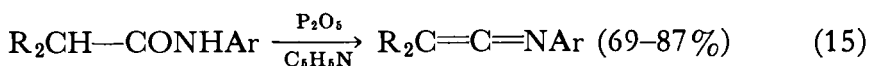
Substituted amides are also often converted to nitriles by the action of phosphorus pentachloride and similar reagents, with concomitant loss

of the N-substituents (von Braun reaction) (Eq. 14). This is particularly

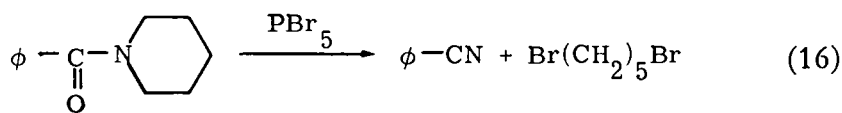


effective with benzamides, and provides a useful way of replacing an amino group by halogen.¹³ With most monoalkyl amides, such reactions can be demonstrated to go through imidoyl derivatives, such as imidoyl chlorides, $\text{R}-\text{C}(\text{NR}')\text{Cl}$, and they will be taken up in more detail under that heading.

Phosphorus pentoxide and pyridine convert monosubstituted amides having an α -hydrogen to ketenimines in good yield ^{14a} (Eq. 15).

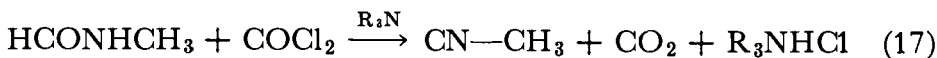


Disubstituted amides cannot, of course, undergo either of the foregoing reactions without suffering dealkylation. They nevertheless react readily with phosphorus pentachloride or pentabromide to give nitriles (Eq. 16).



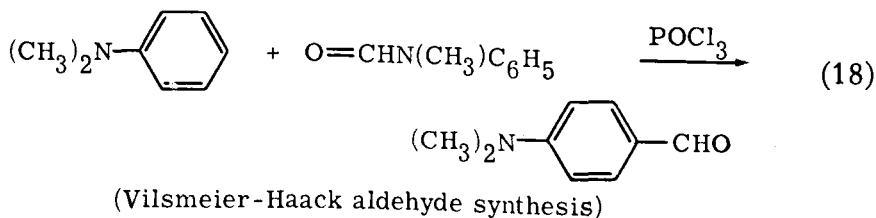
The alkyl groups are removed as alkyl halides, with inversion of configuration when the carbon attached to nitrogen is an asymmetric center.

In the special case of N-monosubstituted formamides, dehydration occurs without loss of the N-substituent, and gives isonitriles ^{14b,c} (Eq. 17).

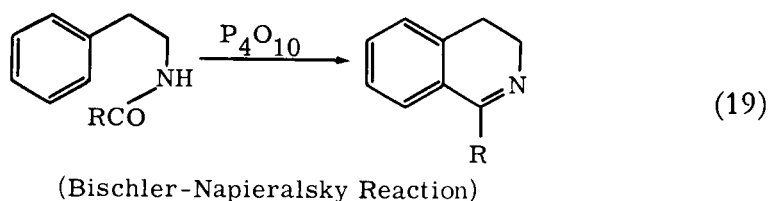


The dehydrating reagents are the usual ones, but they must be used in the presence of an excess of a tertiary amine, and it is probable that here, too, we are actually dealing with dehydrohalogenation of an imidoyl chloride or relative.

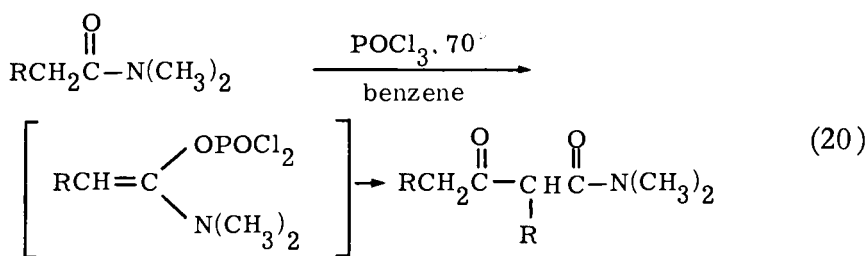
Treatment of substituted amides with dehydrating agents in the presence of reactive aromatic rings may result in ring substitution. This sort of reaction finds useful expression in the Vilsmeier-Haack aldehyde synthesis, in which N-methylformanilide acts as the source of the aldehyde carbon ¹⁵ (Eq. 18). The active agent appears to be an imidic acid



derivative, such as $[R_2N^+=CH-Cl]Cl^-$, in which the carbon atom is very electrophilic. With amides of larger acids, ketones can be prepared, but the method is not widely used. The Bischler-Napieralsky reaction is a cyclic variant, which occurs when β -arylethyl amides are treated with dehydrating agents.¹⁶ It is a useful synthesis of the isoquinoline nucleus (Eq. 19). A related reaction is the self-condensation of dialkylamides,



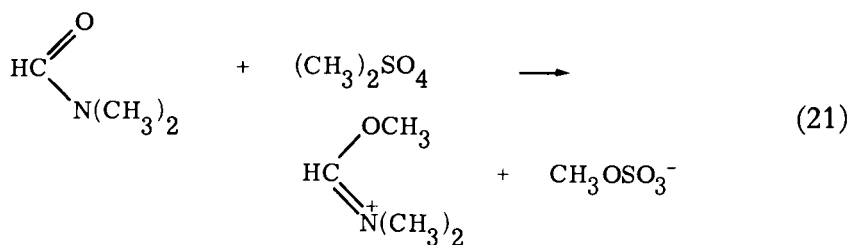
formally analogous to the Claisen self-condensation of esters. The amides first form addition compounds with phosphoryl chloride; when these are heated, β -keto amides are formed in useful yields,¹⁷ presumably through a ketene acetal derivative as a transient intermediate (Eq. 20).



Alkylation Amides in principle provide three sites for the acceptance of an alkyl group: the nitrogen, the oxygen, and the α -carbon. Examples of all three possibilities are known, but they have seen only quite limited synthetic applications (compare, however, the alkylation of imides in the Gabriel phthalimide synthesis, p. 156).

Under neutral conditions, amides in general react sluggishly with alkylating agents, and only those more active than alkyl halides, such as

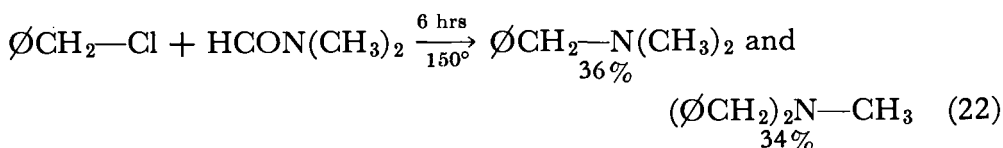
alkyl sulfates or oxonium salts, $R_3O^+ BF_4^-$, are effective. Substitution occurs on oxygen, giving alkyl imidates (imido esters)¹⁸ (Eq. 21). It



is interesting that in this reaction the usual dominating nucleophilicity

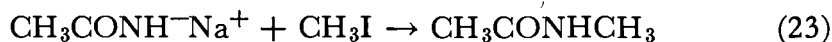
of N over O is ineffective. This is presumably a consequence of the fact that in the amido group, the N and O are not electronically independent, but the group must be considered as a unit, as has been pointed out in connection with basicity also. Alkylation on oxygen gives an ion in which delocalization of the charge is possible; in the N-alkylated isomer,

$\text{R}-\text{CO}-\overset{+}{\text{N}}\text{R}_3$, such delocalization cannot occur. An apparent exception to preferred O-alkylation is the formation of benzyldimethylamine from benzyl chloride and dimethylformamide ^{19a} (Eq. 22). Since this



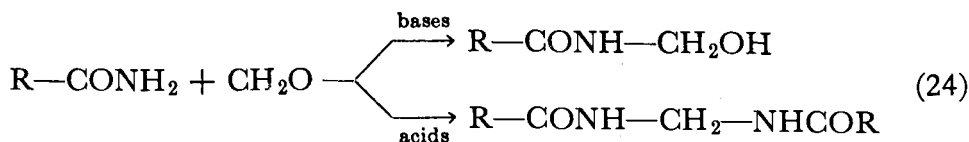
reaction is slow and requires a temperature of 150° , it is likely that the product ultimately observed arises from reactions subsequent and perhaps parasitic to initial O-alkylation.

Alkylation of carboxamide anions (i.e., the sodium salts) with alkyl halides alkylates the nitrogen, giving more highly substituted amides (Eq. 23). The α -carbon is unaffected in simple amides; only when



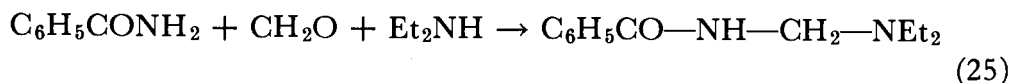
there are additional structural features present that increase the acidity of the α -hydrogens, as in acetoacetamide, $\text{CH}_3\text{COCH}_2\text{CONH}_2$, or phenylacetanilide, does alkylation of the carbanion compete successfully with alkylation of the carboxamide anion.^{19b} It is to be noted that alkylation of the carboxamide ion on either nitrogen or oxygen produces a neutral molecule (N-alkyl amide or imidate ester), and the greater intrinsic nucleophilicity of nitrogen is then able to determine the course of the reaction, in contrast to the alkylation of neutral amide molecules.

Aldehydes and ketones Aldehydes will usually react with amides containing an N—H, but ketones are in general nearly unreactive. In neutral or basic solution, amides undergo simple addition to the aldehyde carbonyl, producing amides of carbinolamines.²⁰ Acid catalyzes dehydration and further coupling, and the products are commonly methylenediamine derivatives (Eq. 24). The reaction of formaldehyde with amide

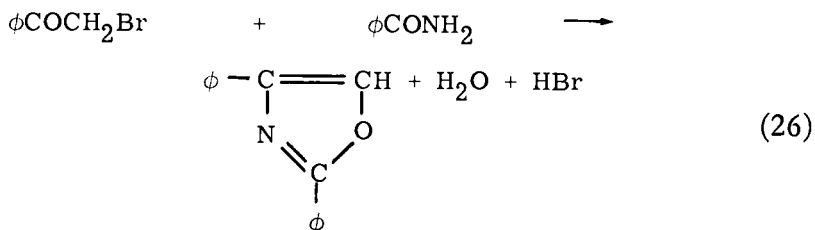


groups is the basis of its preservative action on animal tissue.

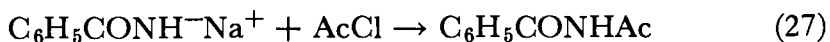
In a variant of these reactions, a process resembling the Mannich reaction can take place (Eq. 25). α -Halo aldehydes and even ketones



can react with ring closure; presumably the first step is alkylation of amide oxygen by the halide-bearing carbon. This and similar reactions are of great importance in the synthesis of heterocyclic compounds (Eq. 26).



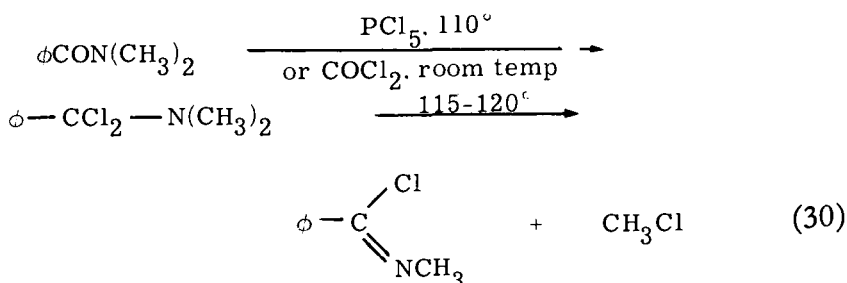
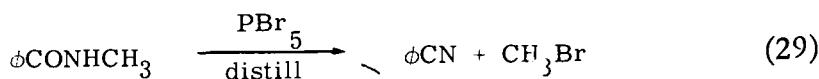
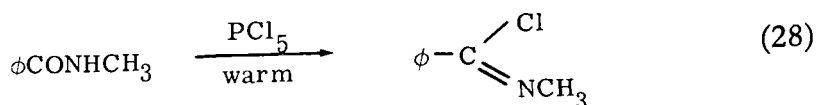
Acylation Acylation of amides occurs only with the more powerful reagents, such as anhydrides and acyl halides, inorganic and organic. These substances are all dehydrating agents at the same time, with the result that three distinct types of products may be obtained: those in which N—H is converted to N-acyl; those in which the amide oxygen is replaced by halogen or sulfur, and those in which nitriles result from removal of the elements of water. Which will occur in a given instance depends not only on the reagent used, but very much on the conditions. There is much evidence to suggest that the initial step in every case is acylation of (or "complex formation" with) the amide oxygen, followed by rearrangement, elimination, or both. Acid anhydrides and halides give isolable acylation products with amides principally when used in the presence of base, and at mild temperatures (Eq. 27). Mixed imides can



be prepared in this way, but symmetrical imides and nitriles take their place when the conditions are too strenuous.

At moderate temperatures, acylation of monoalkyl- and dialkyl-amides by phosphorus halides can be stopped at a stage before loss of alkyl groups; in such cases, the amide oxygen is replaced by halogen from the dehydrating agent (usually phosphorus pentachloride) (Eqs. 28–30). Phosphorus "pentasulfide" (actually P_4S_{10}), replaces amide oxygen by sulfur, giving thionamides (qv).

Nitrosating agents form a special case. They react with amido groups containing $-\text{NH}_2$ and $-\text{NHR}$, but not at all as readily²¹ as they do with primary and secondary amines, since amides are much poorer nucleophiles. The general reaction of unsubstituted amides with nitrous acid



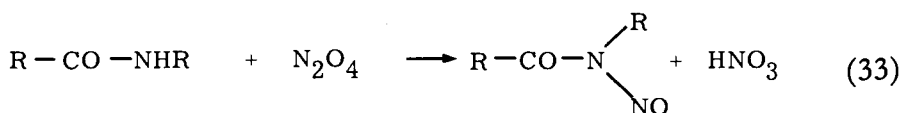
is to give nitrogen and the carboxylic acid ^{21a} (Eq. 31), but owing to the



sluggishness of many amides, it is not always a useful process; butyl nitrite gives nearly quantitative yields, however ^{21b,c} (Eq. 32). Substituted

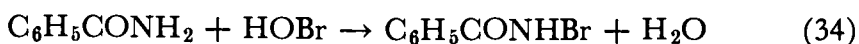


amides are converted to N-nitroso amides with varying ease ^{21d}; nitrogen tetroxide (Eq. 33) and nitrosyl chloride are the most reliable reagents,



but in some cases even aqueous nitrous acid is successful. The N-nitroso amides are highly reactive substances, whose chemistry is discussed further in Chapters 11 and 15.

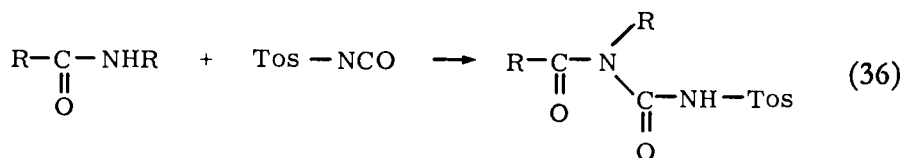
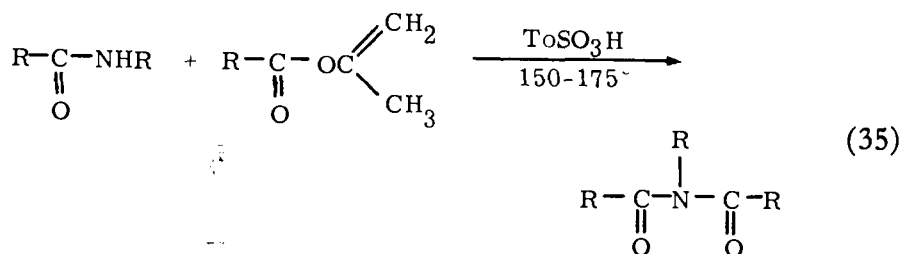
Halogens and hypohalous acids function as acylating agents toward amides bearing an N—H; the reactions are ionic processes analogous to other acylations, and are not related to the free-radical halogenation of saturated hydrocarbons. N-Halogenation of amides usually occurs very easily, often in cold aqueous solution (Eq. 34). The resulting N-halo



amides are intermediates in the Hofmann degradation of unsubstituted amides to amines of one less carbon; their chemistry is discussed in a later section of this chapter.

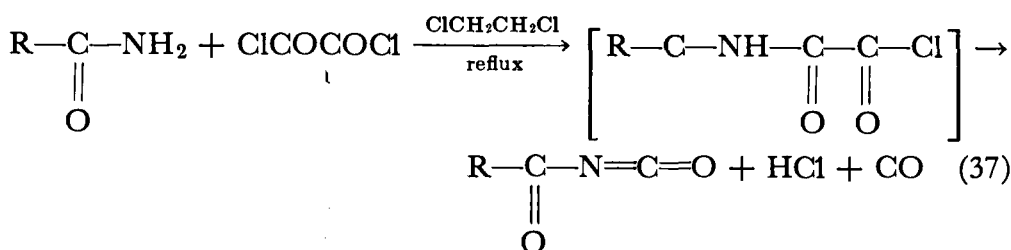
Amides can also be acylated with ketenes, ^{22a} isopropenyl esters, ^{22b} and

isocyanates ^{22c} (Eqs. 35, 36). The isopropenyl ester method is apparently

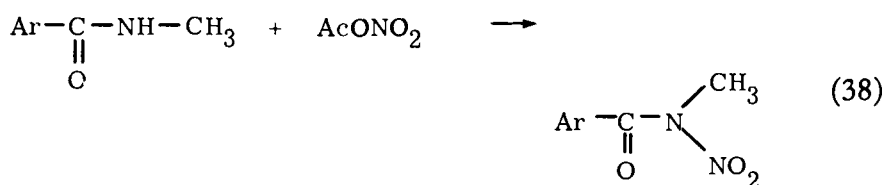


a general one for the preparation of unsymmetrical imides.

Oxalyl chloride accomplishes more than simple acylation when heated with primary amides, and acyl isocyanates are produced in moderate to good yields ^{22d} (Eq. 37).



N-Alkyl amides can be nitrated on the nitrogen by acetyl nitrate (but not by other classes of nitrating agents) ^{22e} (Eq. 38). Unsubstituted

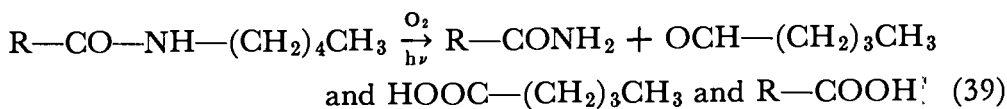


amides are converted to carboxylic acids, probably through unstable N-nitro intermediates.

The reaction of diazonium salts on amides, which produces 1-aryl-3-acyl triazenes, $\text{Ar}-\text{N}=\text{N}-\text{NHCOR}$, can be considered as a related example of electrophilic attack (see Chapter 11).

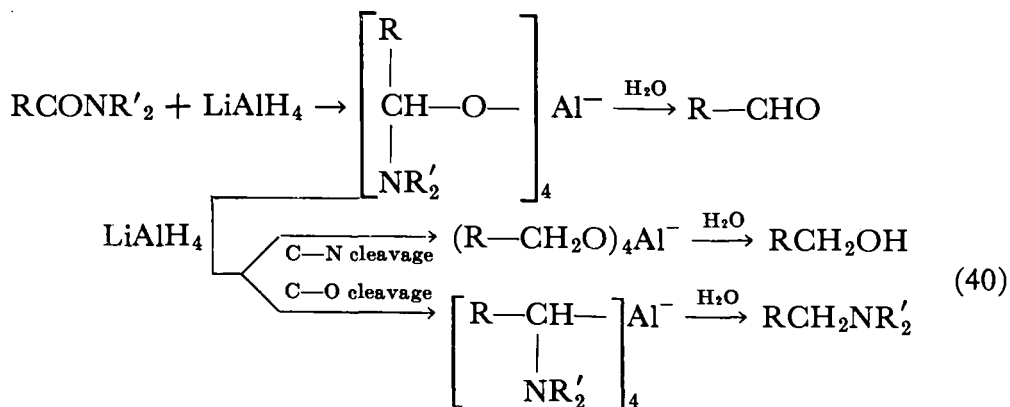
Oxidation and reduction of amides occur, but only reduction is of importance. Amides are moderately resistant to both processes, however, and it is usually possible to oxidize or reduce other functions without disturbing an amido group. Photocatalyzed oxidation by oxygen principally attacks the N-alkyl group, at the 1-position, giving products similar to those obtainable from the corresponding amine; the C—N

bond is cleaved, and aldehydes (or ketones), primary amides, and carboxylic acids are produced ²³ (Eq. 39).



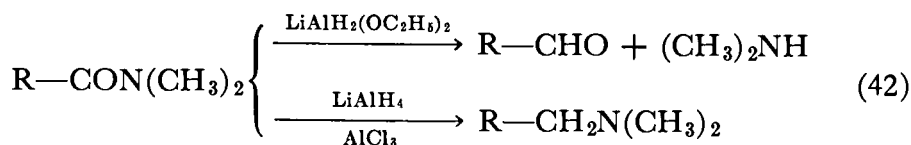
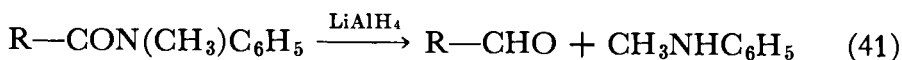
Reduction Reduction of amides has been mentioned in Chapter 2 as a useful preparative method for amines. Mild reducing agents do not affect amides. Electrolytic reduction,²⁴ usually with lead or zinc-amalgam electrodes in sulfuric acid solution, used to be the best method, although it is generally successful only with amides of aromatic acids and with dialkylamides of aliphatic acids. Hydrogenation can also be useful, but the general inertness of amides makes high pressures and temperatures necessary. Recent studies²⁵ have shown rhenium to be an unusually effective catalyst, however. Sodium and hot alcohol, a reducing system of wide application, is of very limited value with amides. Many amides are little affected, and those that do react undergo C—N cleavage to a major extent, producing the alcohol derived from the acyl group. So-called Birch reduction—sodium, calcium, etc., in liquid ammonia plus a proton source, such as alcohols—produces aldehydes,²⁶ and serves as a useful deacylating method.

The metal hydrides, essentially lithium aluminum hydride and its derivatives, are the foremost reducing agents for amides. With proper choice of reagent and proportions, either amines or aldehydes can be obtained in preparatively useful yields (Eq. 40). Reduction apparently



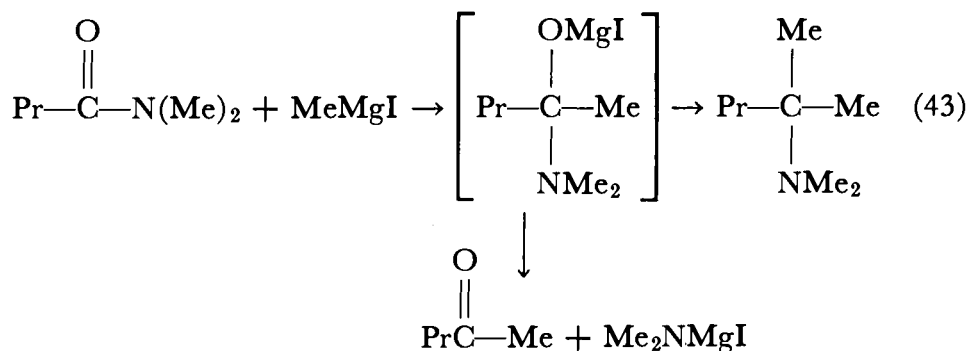
goes in two stages, first by addition of hydride to the carbonyl group, forming a carbinolamine (as its aluminate complex), which can be hydrolyzed to an aldehyde. In the next stage, either a C—N or a C—O bond must be broken, resulting respectively in an alcohol, or an amine. Of course, it is only when the first stage is faster than the second that it is possible to stop the reduction at the carbinolamine stage for the purpose of aldehyde synthesis. Such conditions prevail with N-methylanilides in general when lithium aluminum hydride is used,²⁷ and with dialkyl

amides when lithium diethoxyaluminum hydride, $\text{LiAlH}_2(\text{OC}_2\text{H}_5)_2$, is the reducing agent ²⁸ (Eqs. 41, 42). Anhydrous aluminum chloride

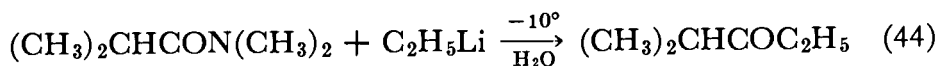


used with lithium aluminum hydride greatly favors C—O cleavage in the second reduction stage, and thus improves the conversion of amides to amines ²⁹ (Eq. 42). Unsubstituted amides appear to be dehydrated in the first stage of reaction with lithium aluminum hydride, giving nitriles, which are, of course, reduced rapidly to amines.³⁰ With such a reaction path, aldehyde formation of the type described above cannot occur, and yields of amines are accordingly high.

Organometallics The reactions of organometallic reagents with amides are of the simple acid-base type when a hydrogen is present on nitrogen, and the reagent is destroyed by conversion to hydrocarbon. With N,N-disubstituted amides, addition to the carbonyl group might be expected, analogous to the reaction of Grignard reagents with esters. The amide carbonyl is much less reactive, however, and some reaction with the α -hydrogens apparently occurs in some cases, converting all or part of the organometallic reagent to hydrocarbon.³¹ Some ketone is formed from the addition of one equivalent of Grignard reagent; some amine, resulting from the addition of two equivalents, may be formed (Eq. 43), but it is not clear how the second addition takes place. The



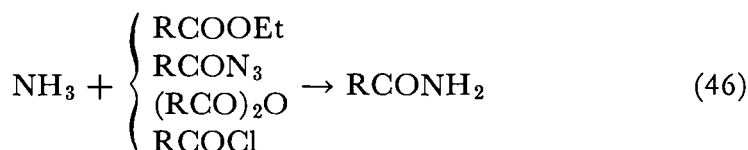
reactions have so far seen little preparative use, although the reaction of alkyllithium compounds with dimethylamides can give good yields of ketones ^{31a,b, 32a} (Eq. 44), and dimethylformamide gives aldehydes with



Grignard reagents.^{32b}

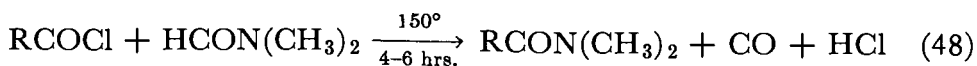
PREPARATION Most preparative reactions for amides fall into four classes: acylation of amines, hydration of nitriles, oxidation, and rearrangements. Although all are significant, the first is by far the most widely used.

Acylation of ammonia and amines has been discussed in Chapter 2 in connection with reactions of amines. It can be accomplished with carboxylic acids by heating their amine salts,³³ and with esters,³³ acyl azides,^{33d} anhydrides,^{33e} and acid halides,^{33d} in order of increasing vigor (Eqs. 45, 46). Ketenes can also be used (Eq. 47), but, of course, are not as easily obtainable. An improved method for converting acids to amides is to treat them simultaneously with a carbodiimide and an amine (see Chapter 6). These methods are obviously applicable to the prepa-



ration of both substituted and unsubstituted amides, and have seen extensive application in peptide synthesis.^{33d,e}

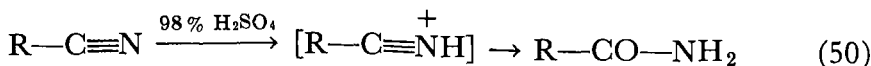
Acids, esters, and nitriles can also be converted to amides by an exchange reaction with formamide, accomplished by simple refluxing,³⁴ and acid chlorides and anhydrides can be converted to dimethylamides by heating with dimethylformamide in the presence of a trace of sulfuric acid¹⁹ (Eq. 48). Such methods have the notable advantage of avoiding



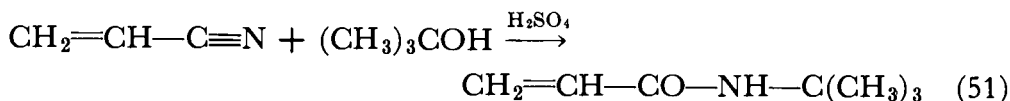
the handling of noxious amines. Acids can also be converted to amides by heating with urea or thiourea^{35, 36} (Eq. 49).



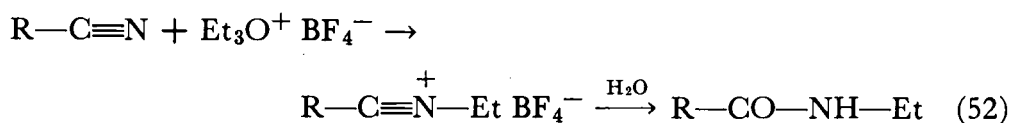
Hydration of nitriles¹² to amides may be simple or alkylative. Ordinary hydrolytic procedures applied to nitriles usually accomplish further hydrolysis of the amides first formed, but cold concentrated sulfuric or hydrochloric acid effectively hydrates nitriles to amides without significant further hydrolysis (Eq. 50). Even formamide can be prepared in this way, from hydrogen cyanide. If tertiary alcohols (or olefins derived from



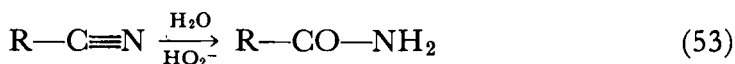
them) are present, the nitrogen is alkylated during the hydration process, and monosubstituted amides are produced (Eq. 51) (Ritter reaction,



see Chapter 5.) It is a reaction of some commercial importance. Alkyl groups that form carbonium ions less readily can also be added to nitriles, but more powerful reagents, such as the trialkyloxonium salts, are required ³⁷ (Eq. 52).

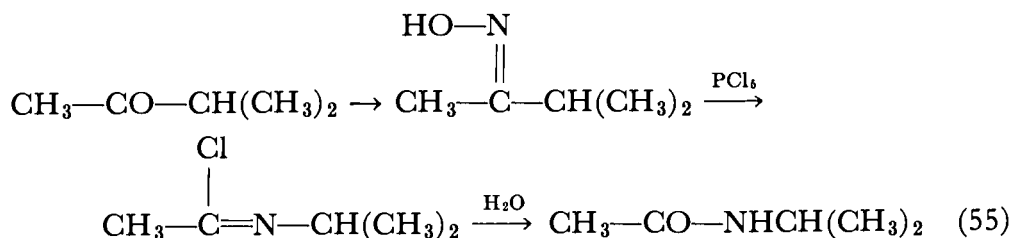
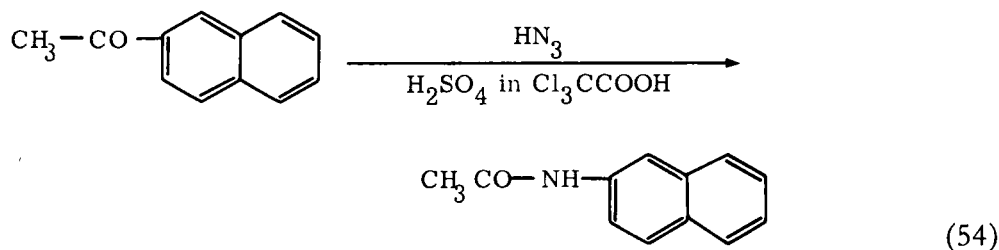


An alternative method for hydrolyzing nitriles to amides is to use alkaline hydrogen peroxide solution (Eq. 53). The hydroperoxide anion,



HO_2^- , is a much stronger nucleophile than hydroxide ion (even though it is not as strong a base), and is the initial attacking agent. This method is not as generally successful as the sulfuric acid method.

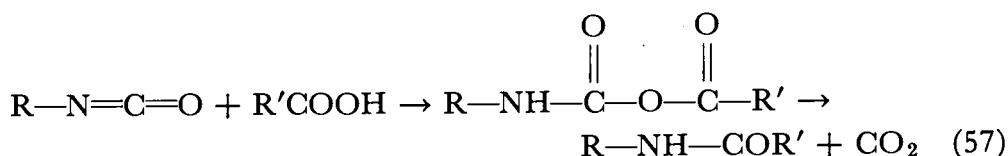
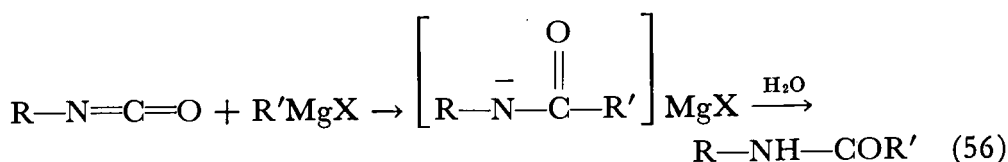
Monosubstituted amides can be prepared in great variety by the Beckmann rearrangement of ketoximes, and the analogous Schmidt reaction between ketones and hydrogen azide (Eqs. 54, 55). Unsym-



metrical ketones or oximes may give mixtures of isomeric amides, but when one group is aryl, an anilide is almost always the major if not the exclusive product. The Beckmann rearrangement is discussed more fully in Chapter 8, and the Schmidt reaction in Chapter 10.

There are a number of less important reactions leading to amides, such as the addition of Grignard reagents or carboxylic acids to iso-

cyanates (see Chapter 6) (Eqs. 56, 57). In the latter, a mixed carbamic-



carboxylic anhydride is first formed, and then loses carbon dioxide.

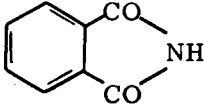
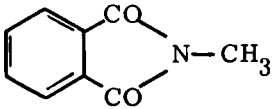
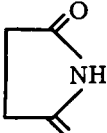
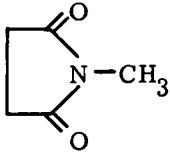
B. Diacylamides, Imides, and Triacylamides

NOMENCLATURE AND PROPERTIES Acid imides, or diacylamides, and triacylamides are named simply by enumerating the acyl groups; for example, $(\text{CH}_3\text{CO})_2\text{NH}$ is diacetamide, HCONHCOCH_3 is N-formylacetamide, and $(\text{CH}_3\text{CO})_3\text{N}$ is triacetamide. The terms "secondary" and "tertiary" have sometimes been used for diacylamides and triacylamides, but they are more generally used to indicate total degree of substitution on nitrogen, and should not be used in naming specific compounds. The ending "-imide" is used with cyclic diacylamides, such as in "succinimide" and "cyclopentane-1,2-dicarboximide."

Diacylamides having a free NH are nearly all solids, and have high boiling points, indicating the presence of appreciable hydrogen bonding. Only the smaller ones can be distilled without decomposition, and the smallest, diformamide, is known only in the form of its salts. Substitution of the nitrogen removes the possibility of hydrogen bonding, and the melting point is lowered, as is the boiling point also if the molecular weight of the substituent is small. Representative examples are given in Table 4-2. The smaller diacylamides are quite soluble in water, and also soluble even in ether to some extent. Phthalimide, however, perhaps the most commonly encountered imide, is only very slightly soluble in water or common organic solvents (but dissolves to the extent of 14% in cold pyridine). The high melting and boiling points and low solubility of cyclic imides is apparently due to the fixed orientation of the dipoles in the imide system, analogous to the similar effect observed in comparing open-chain esters with lactones.

The addition of a second acyl group to ammonia further changes the acid-base properties in the same direction as the first one, but not quite to the same degree. Diacylamides no longer show the feeble basic properties of monoacylamides, and this fact can be used to separate the two classes from their mixtures (dry hydrogen chloride in an organic solvent such as benzene has been used). The acid strength of monoacylamides, which is slightly less than water, is further increased by about 5 to 6 powers of 10, and unsubstituted diacylamides are distinctly acid in the

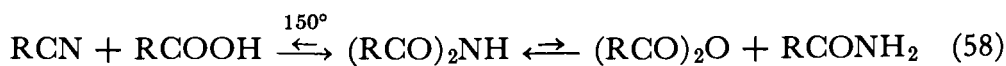
Table 4-2 *Physical properties of some diacyl- and triacylamides*

	mp	bp
HCONHCOCH_3	70°	
$(\text{CH}_3\text{CO})_2\text{NH}$	79°	223°
$(\text{CH}_3\text{CO})_2\text{NCH}_3$	liq.	192°
$(\text{C}_6\text{H}_5\text{CO})_2\text{NH}$	148°	
$(\text{C}_6\text{H}_5\text{CO})_2\text{N}-\text{CH}_3$	95°	
	238°	
	134°	
	126°	288°
	70°	235°
$(\text{CH}_3\text{CO})_3\text{N}$	78°	
$(\text{CH}_3\text{CO})_2\text{NCHO}$	107°	
$(\text{C}_6\text{H}_5\text{CO})_3\text{N}$	208°	subl.

presence of water, similar to phenols. Succinimide has $\text{p}K_{\text{a}}$ 9.66, and glutarimide, $\text{p}K_{\text{a}}$ 11.43. Triacylamines, naturally, are completely neutral compounds.

REACTIONS Diacylamides having a free N—H can obviously form salts readily, even in water solution. N-Substituted diacylamides and triacylamides are not known to form salts of any kind.

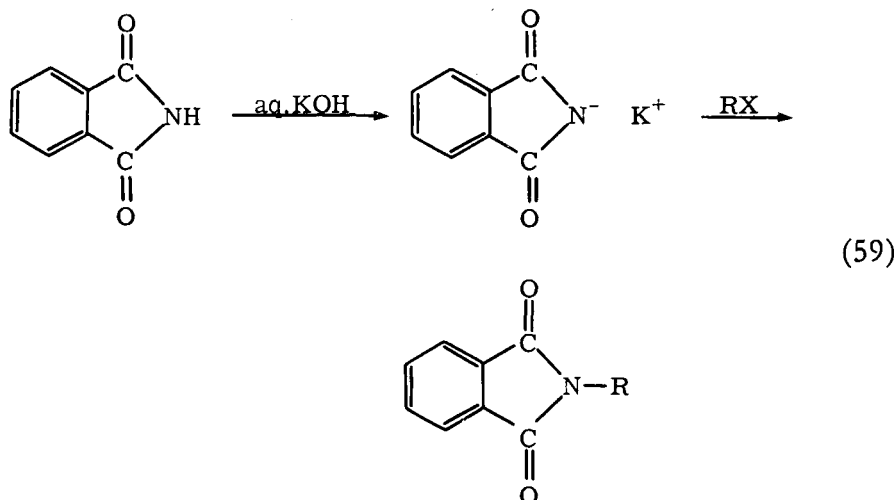
Strong heating of unsubstituted diacylamides sets up a multiple equilibrium (Eq. 58). The first phase is formation of nitrile and carboxylic



acid; the acid can then react with more diacylamide to form an anhydride and a simple amide.³⁸ With unsymmetrical diacylamides, such equilibria provide a pathway for disproportionation into symmetrical diacylamides. Mixed carboxyl carbonimidyl anhydrides, $\text{RCO}-\text{O}-\text{C}(\text{NH})\text{R}$, probably function as intermediates.

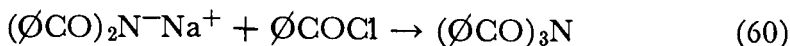
Diacyl- and triacylamides are mild acylating agents and are easily hydrolyzed in stages, the acyl groups becoming successively more difficult to remove. These compounds will thus acylate amines, and can be alcoholized to esters.

Salts of diacylamides can be alkylated with the usual alkylating agents, and this process is an essential step in the Gabriel phthalimide synthesis of primary amines (Eq. 59). Diacylamide anions are not strongly nucleo-

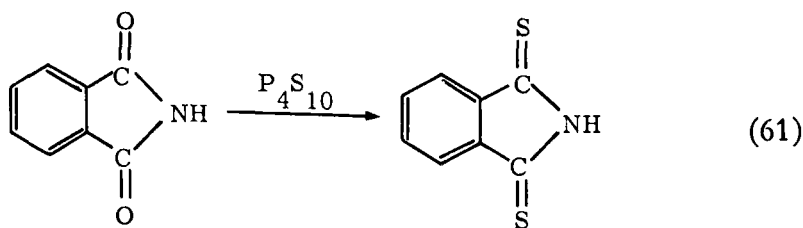


philic, however, and the alkylation reactions are often slow, requiring moderate heating for completion in a reasonable time. This often necessitates sealed tubes or autoclaves with the smaller alkyl halides. However, the reaction is readily accomplished in dimethylformamide solution (see Chapter 2, Gabriel Synthesis). Alkylation of diacylamides with diazomethane is also possible,³⁹ but a significant part of the alkylation may then occur on oxygen.

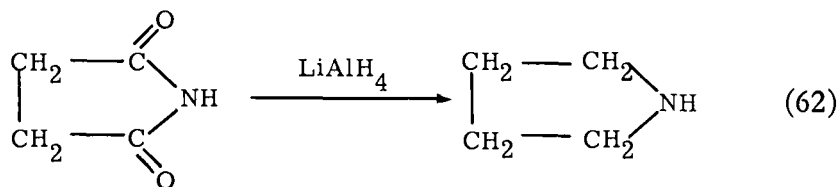
Acylation of diacylamides, usually in the form of their salts, is accomplished with acid chlorides, and is a convenient synthesis of triacylamides (Eq. 60). It may be carried out in the same step as the formation of the



diacylamide, by treatment of lithium nitride, which is easily obtainable, with acid chlorides.⁴⁰ Inorganic acid halides and anhydrides, on the other hand, behave toward diacylamides principally as dehydrating agents. Phosphorus pentasulfide exchanges sulfur for oxygen, giving thioimide derivatives⁴¹ (Eq. 61).

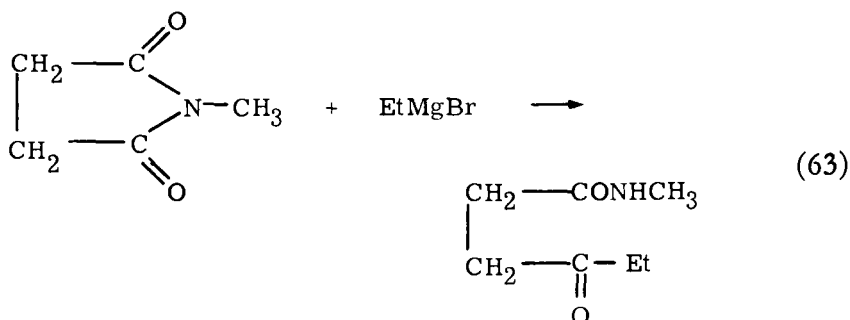


Reduction of diacylamides is in general possible, but its practical use is essentially confined to cyclic imides, which give heterocyclic reduction products. The best reagent appears to be lithium aluminum hydride, which converts succinimides to pyrrolidines, for example ⁴² (Eq. 62).



Hydrogenation requires unusually severe conditions, and zinc (in the presence of acid or base) reduces only one carbonyl group.

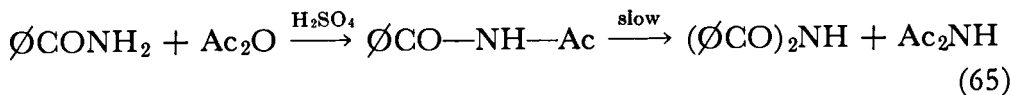
Diacylamides that bear an N-substituent will react with organometallic reagents at the carbonyl groups. ⁴³ Ketones can be prepared in this way, and the reaction has interesting synthetic possibilities when applied to cyclic imides, which give keto amides, among other products (Eq. 63).



PREPARATION Unsubstituted diacylamides can be prepared in variety by the reaction of amides with sodium or potassium metal (Eq. 64),

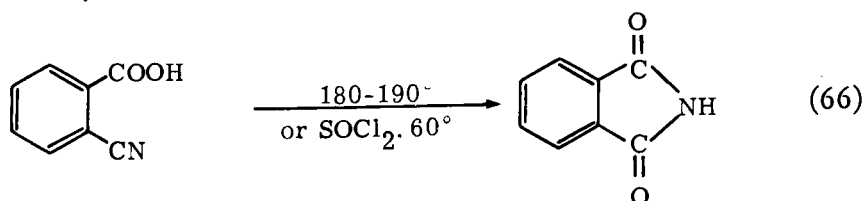


as has been explained in the section dealing with amides. They may also be prepared by acylation of amides, using acid chlorides, acid anhydrides, isopropenyl esters, ^{22b} or ketenes; both basic catalysts (e.g., pyridine) and acid catalysts (e.g., H_2SO_4) are effective ⁴⁴ (Eq. 65). The

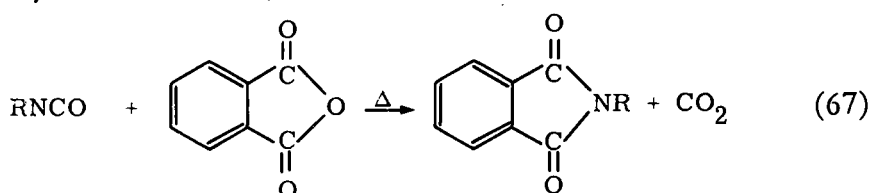


equilibrium reaction between carboxylic acids and nitriles on heating favors the corresponding diacylamide, and can be used for preparative purposes. The reaction may occur between separate molecules, ³⁸ or internally, as in the conversion of *o*-cyanobenzoic acid to phthalimide

(Eq. 66). Diacylamides can also be prepared, with variable success, by



heating isocyanates with anhydrides ⁴⁴ (Eq. 67).



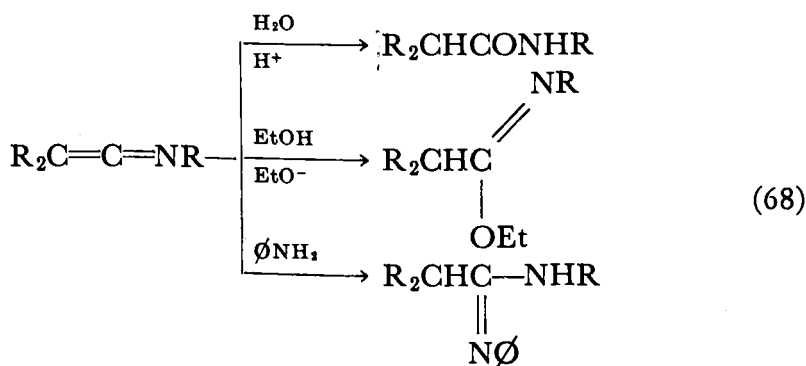
C. Ketenimines

Ketenimines are, as their name implies, the nitrogen analogues of the ketenes, and are characterized by the structure $\text{C}=\text{C}=\text{N}-$. Since

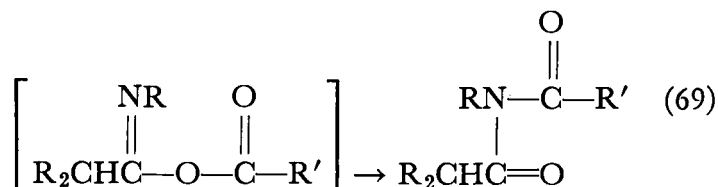
the central dicoordinate carbon becomes a carbonyl carbon on hydration, making an amide, these compounds can be considered as amide derivatives. They are all named as substitution derivatives of ketenimine, $\text{CH}_2=\text{C}=\text{NH}$; $(\text{CH}_3)_2\text{C}=\text{C}=\text{N}-\text{O}$ is thus "N-phenyldimethylketenimine" or "dimethylketen-N-phenylimine."

The smaller alkyl ketenimines resinify very easily, and have not been isolated pure. Most known ketenimines ^{30, 45} are oils or low-melting solids, distillable under high vacuum; they are colorless or light yellow. Infrared absorption at $2000-2050 \text{ cm}^{-1}$ is found in all ketenimines, and is characteristic of the cumulative double-bond system.

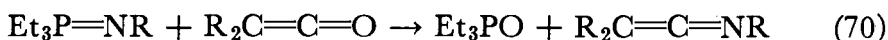
The reactions of ketenimines are roughly parallel to those of ketenes, but the reactivity is not so great, and some reactions of ketenes have not been observed with ketenimines. Addition to the double-bond system to give carboxyl derivatives is the dominant chemical behavior ⁴⁶ (Eq. 68).



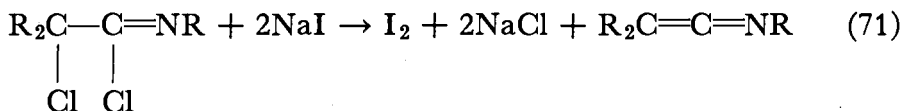
Water alone reacts only very slowly with ketenimines, but traces of acid catalyze rapid conversion to amides. Alcohols also react only slowly, but addition to form imidate esters is catalyzed by alkoxides. Amines react readily, giving amidines. The addition of carboxylic acids appears to give carbonyl imidoyl mixed anhydrides, but the acyl group migrates rapidly from oxygen to nitrogen (Chapman rearrangement), giving diacylamides (Eq. 69).



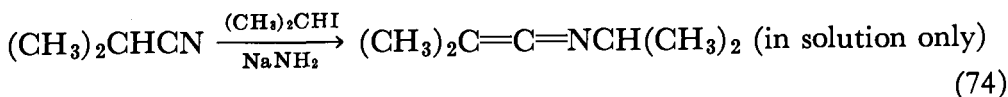
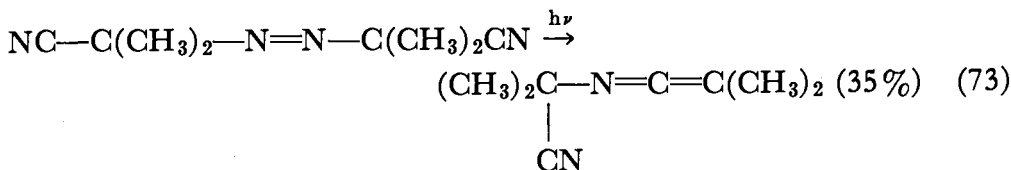
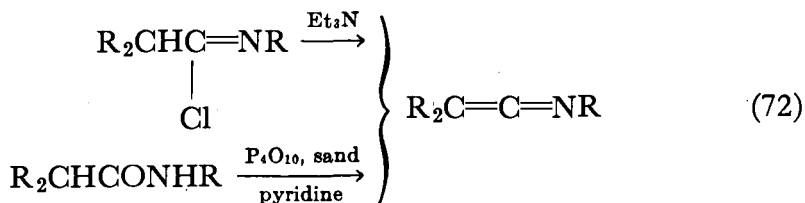
Ketenimines were originally prepared by the reaction of ketenes with phosphine imines, and later with phosphimides^{47a} (Eq. 70). The



dehalogenation of α -chloroimidoyl chlorides⁴⁵ by means of sodium iodide is a convenient synthesis introduced more recently (Eq. 71). This reac-



tion is reversible; chlorine will add to ketenimines to generate α -chloroimidoyl chlorides. Ketenimines can also be made by dehydrohalogenation of imidoyl chlorides with tertiary amines,^{46b} by the dehydration of secondary amides,^{47b} by the photolysis of α,α -azo-bis-nitriles,^{47c,d} and in certain special cases by the alkylation of nitrile anions, as described in Chapter 5 (Eqs. 72-74).

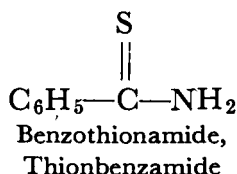
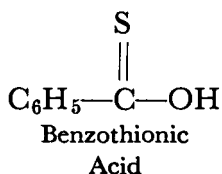
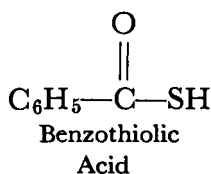


D. Thionamides

NOMENCLATURE AND GENERAL REMARKS Thionamides are named according to the name of the corresponding ordinary amide, the presence of sulfur in place of oxygen being indicated. Although the simple prefix "thio-" can be very useful to indicate the presence of sulfur in a compound, usually replacing oxygen, it can also be ambiguous. Accordingly, the

preferred I.U.C. nomenclature for amides in which $\text{C}=\text{O}$ has become

$\text{C}=\text{S}$ uses "thion," either as a prefix ("thionacetamide") or as an infix ("acetothionamide"). By this device it is possible to name such compounds as $\text{CH}_3\text{OC}_6\text{H}_4\text{CSNH}_2$, "anisothionamide," and $\text{HOCH}_2\text{CSNH}_2$, "glycolothionamide," with complete clarity as to which oxygen has been replaced by sulfur. The infix "thion" comes from the name of the parent acid, whose tautomers can be named distinctly where necessary.



PROPERTIES, OCCURRENCE, AND USE The unsubstituted thionamides are solids, and thionformamide, mp 29° , and thionacetamide, mp 116° , melt at distinctly higher temperatures than their oxygen analogues. Substitution on the nitrogen generally lowers the mp, and dimethylthionformamide is a liquid, bp 228° . The smaller thionamides are quite

soluble in water. The $\text{C}=\text{S}$ grouping shows ultraviolet absorption

that is both stronger than that of $\text{C}=\text{O}$, and closer to the visible.

Although simple thionamides are colorless, some thionamides have a light yellow to red color, owing to tailing of the peak in the near ultraviolet into the visible region. The appearance of color is influenced by substitution on the nitrogen as well as by other factors.⁴⁸

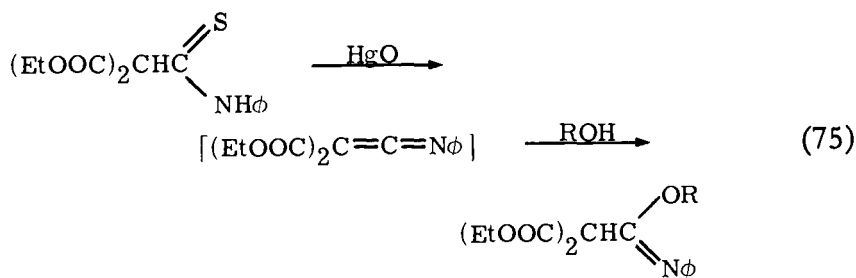
Most thionamides are essentially neutral in water solution although their acidity is appreciably greater than ordinary amides; thioanilides and thionamides of the stronger acids (e.g., thionformamide) will form salts in aqueous solution. Their basicity appears to be similar to ordinary

amides, for most thionamides are capable of forming hydrochlorides in the absence of water.

The thionamide group does not have important natural occurrence. The vitamin thiamine, which contains a thiazole ring, is a derivative of a thionamide, however. On the other hand, a wide variety of thionamides have a diversity of industrial uses, both as end products, such as for the acceleration of the vulcanization of rubber, and as intermediates, particularly in the synthesis of vitamins and drugs, both heterocyclic and open chain. Their greatest chemical importance seems to be as intermediates for the synthesis of thiazoles and thiazolines. Thionacetamide has use as an *in situ* source of hydrogen sulfide for precipitation reactions in inorganic qualitative analysis.

REACTIONS ⁴⁹ The chemistry of thionamides is dominated by the sulfur atom, and although there are many close similarities to ordinary amides, there are also many important differences, both quantitative and qualitative.

Thionamides form sodium or potassium salts by direct reaction with the metals in the absence of water, but heavy metal salts react with thionamides even in water solution, either forming complexes or replacing sulfur with oxygen and precipitating the metal sulfides. In certain cases, at least, it appears that the removal of the elements of hydrogen sulfide by mercuric oxide gives ketenimines as the initial products,^{50a} which then react with available nucleophiles, such as water, alcohols, etc., to give amides, imidate esters, etc. (Eq. 75). Complex formation is particularly

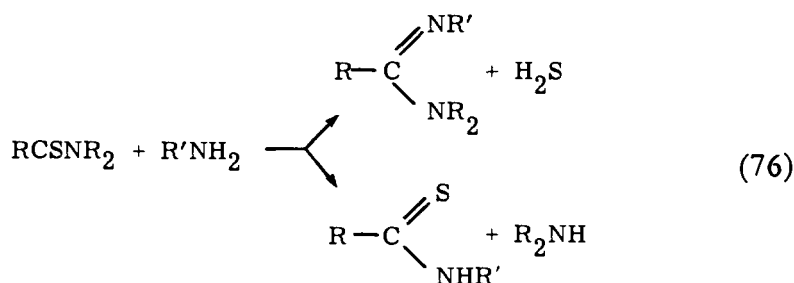


pronounced in the case of dithionoxamide, $\text{H}_2\text{NCSCSNH}_2$, which forms colored products, often insoluble in water, and this and other thionamides have been used for both qualitative and quantitative determination of various metals, particularly of the transition series.^{50b}

Hydrolysis of thionamides, catalyzed by either acid or base, goes all the way to carboxylic acids. It is only rarely possible to stop at the intermediate amide stage, and it appears that amides may be hydrolyzed faster than the corresponding thionamides. Some thionamides are in fact extremely difficult to hydrolyze. Hydrolysis in basic solution occa-

sionally simply removes hydrogen sulfide, producing nitriles. The conversion of thionamides to their oxygen analogues or to carboxylic acids, which is often a required part of a synthetic sequence involving the Willgerodt reaction (see "Preparation"), is frequently best accomplished by indirect means (alkylation to thionimides, or oxidation, discussed ahead).

Solvolysis with other nucleophiles has been studied principally with amines; although a large number of examples have been reported, there are no comprehensive, systematic investigations, and it is difficult to make generalized statements. There are two types of reactions—removal of sulfur (as H_2S), or removal of amino nitrogen (as ammonia or amine) (Eq. 76)—and the circumstances that determine which will occur can be

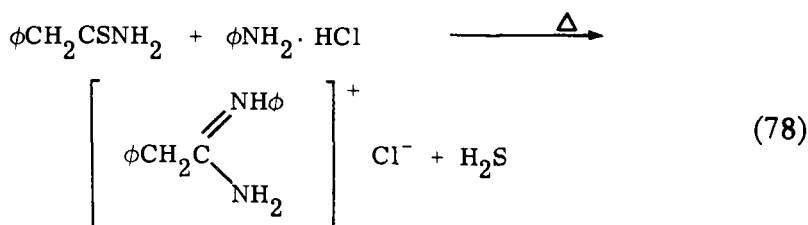


described only roughly.^{49, 51}

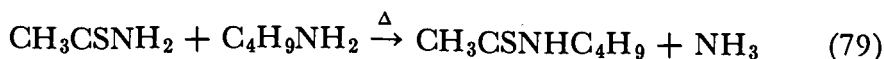
Removal of hydrogen sulfide is the exclusive reaction when unsubstituted thionamides are heated with tertiary amines,^{51a} such as pyridine (Eq. 77). Anilines,^{51b} either free or in the form of salts, generally remove



hydrogen sulfide with the formation of N-aryl amidines (Eq. 78); it should

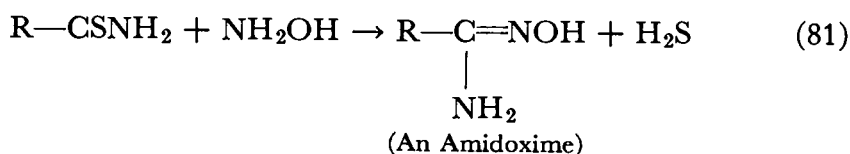
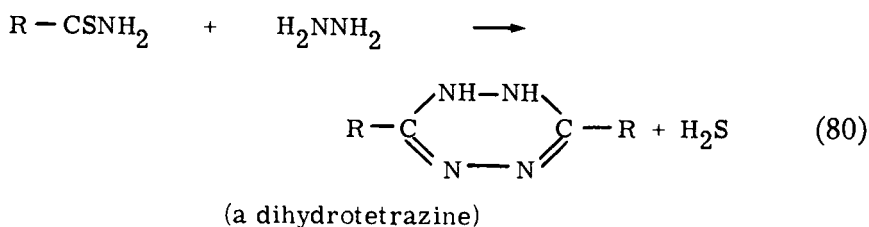


be noted that in this reaction, the products have a C—N double bond conjugated with the aromatic ring. Primary aliphatic amines,^{51c} on the other hand, tend to displace the existing amino group (usually —NH_2), producing substituted thionamides (Eq. 79). Hydrazine^{51d} and hy-



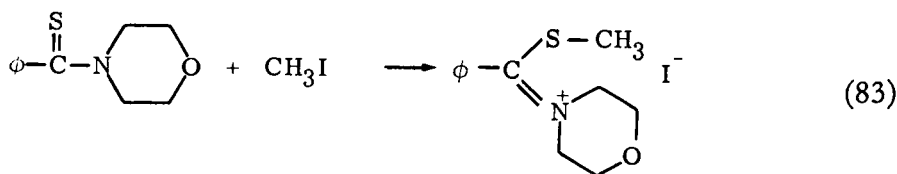
droxylamine^{51e} react like anilines rather than aliphatic amines, and pro-

duce compounds of the amidine type (Eqs. 80, 81). The probably



important role of conditions in determining the course of these reactions does not appear to have been elucidated yet.

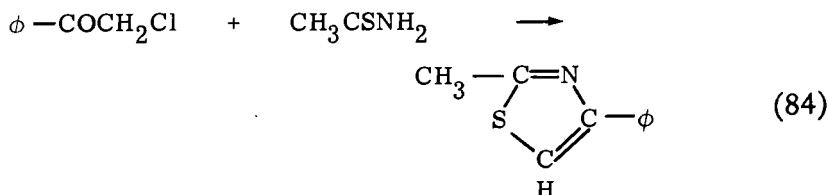
Alkylation of thionamides takes place on sulfur,⁵² giving thiolimidates (Eqs. 82, 83). The site continues to be alkylated even when salts of



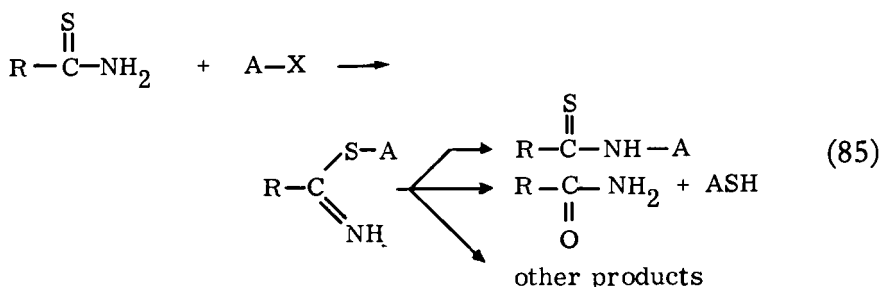
thionamides are used, unlike the situation with ordinary amides. This result is in conformity with the generally greater nucleophilicity of reduced sulfur, and is parallel to the behavior of thiourea and thiocyanate salts. Because of the ease of both S-alkylation and the hydrolysis of the resulting thiolimidates, the sequence provides a useful route for converting thionamides to their hydrolysis products.

The reaction of simple aldehydes and ketones with thionamides has been little studied, but there has been an enormous amount of work with α -halo aldehydes and ketones. The α -carbon alkylates the sulfur, while the carbonyl condenses with the amino group, producing thiazoles (Eq. 84). The reaction occurs even when the nitrogen bears a substituent; N-alkylthiazolium salts are then produced.

The reaction of acylating agents on thionamides has not been systematically studied, although some aspects have received substantial attention. The limited information suggests that the first step is acylation at the sulfur atom, producing thionimidoyl derivatives.^{52a} These may react further by hydrolysis to ordinary amides, by rearrangement to N-acyl



thionamides in analogy with the Chapman rearrangement,^{53a} or by more complex processes involving oxidation-reduction (Eq. 85). Inorganic

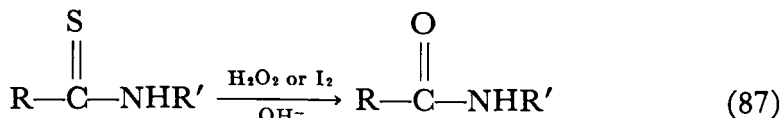


acylating agents, including nitrosating agents and organic sulfonyl chlorides, act partly or entirely as oxidizing agents toward thionamides.

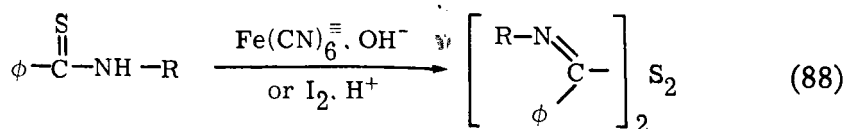
When nitriles are used as acylating agents (in the presence of hydrogen chloride), the intermediate according to this scheme would be a diimidoyl sulfide, $\text{R}-\text{C}(=\text{NH})-\text{S}-\text{C}(=\text{NH})-\text{R}'$. Since the reaction is apparently an equilibrium process, it provides a route for sulfide exchange,^{53b,c} and in this form has been adapted to the synthesis of larger thionamides from nitriles and thionacetamide, the equilibrium being shifted by distillation of acetonitrile, the lowest boiling component^{53c} (Eq. 86).



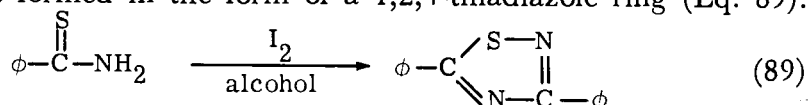
Oxidation of thionamides can take several courses, but all involve the sulfur atom.⁵⁴ Sulfur is removed as sulfate and replaced by oxygen when either iodine^{54a} or hydrogen peroxide^{54b} is used in basic solution (Eq. 87).



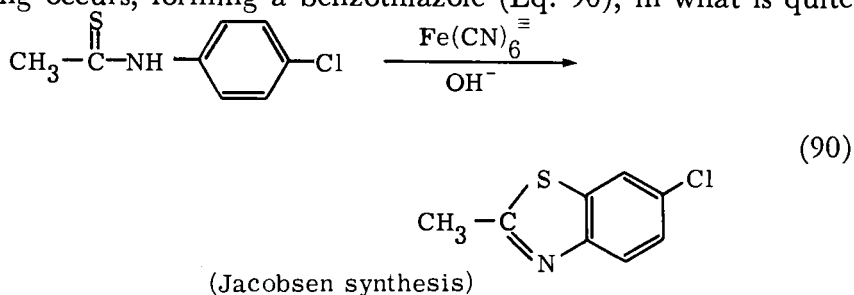
This is a preparatively useful reaction and perhaps the best method to convert thionamides into ordinary amides. Another oxidation path is removal of hydrogen from two molecules of thionamide, producing a diimidoyl sulfide (Eq. 88).^{54c} Removal of one sulfur from two molecules



of thionamide can occur if the nitrogen is unsubstituted ^{54d}, a nitrogen-sulfur bond is formed in the form of a 1,2,4-thiadiazole ring (Eq. 89).



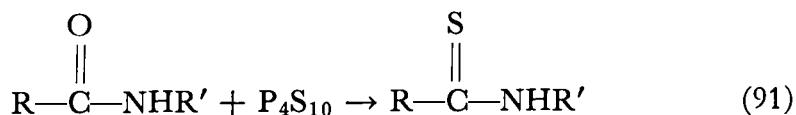
This is a common reaction with thionbenzamide, and occurs at least to some extent with most oxidizing agents. An interesting and synthetically useful cyclization reaction takes place when thionanilides are oxidized by ferricyanide, and some other oxidizing agents; ring closure to the benzene ring occurs, forming a benzothiazole (Eq. 90), in what is quite



possibly a free-radical reaction. It is known as the Jacobsen synthesis. ^{54e}

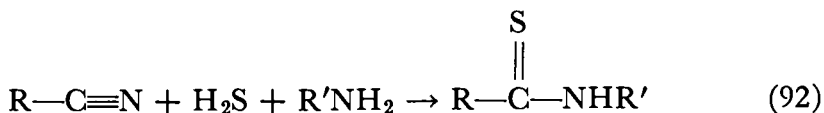
Reduction of thionamides is similar to that of ordinary amides—it is not especially easy, and may give mixtures of products, principally amine and aldehyde. Electrolytic reduction seems to be fairly general as a method of converting thionamides to amines. ^{55a} Dissolving metals, such as zinc and acid, ^{55b} aluminum amalgam, and sodium amalgam, have seen wide but not always satisfactory use. Raney nickel, which in many types of compounds replaces sulfur by hydrogen, appears to convert thionamides more to aldehydes than to amines. ^{55c} A modified nickel hydrogenation catalyst, Adkins-Pavlic W-4, gives better conversion to amines, however. ^{55d} Lithium aluminum hydride appears to react sluggishly, although it has not been widely studied. It reacts with primary thionamides first as an eliminating agent, giving nitriles, analogous to the reaction with ordinary primary amides.

PREPARATION ⁴⁹ Thionamides can be prepared by several quite different types of reactions. The simplest is the direct replacement of oxygen by sulfur in an ordinary amide by heating with phosphorus pentasulfide; it is a fairly general method, but is subject to many interferences (Eq. 91). It can be used to prepare both substituted and unsubstituted



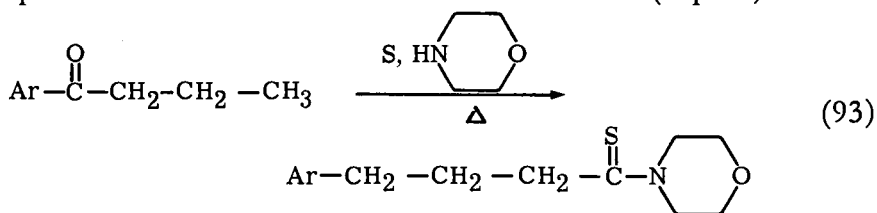
thionamides. The same result can be brought about by converting amides to imidoyl chlorides or similar derivatives, and treating these with hydrogen sulfide. ⁵⁶ Addition of hydrogen sulfide to nitriles in the

presence of base is another simple and general synthetic method; when unsubstituted thionamides are wanted, ammonia is used as the base, whereas substituted thionamides can be obtained by the use of primary amines (Eq. 92). The transfer of hydrogen sulfide from thionacetamide

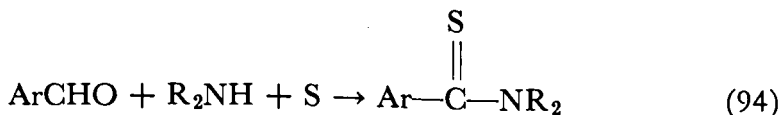


to nitriles under catalysis by hydrogen chloride⁵³ has already been mentioned.

A much more complicated method, of great synthetic value, is the Willgerodt reaction and its Kindler modification, in which aryl alkyl ketones or related compounds are heated with sulfur and ammonia or an amine.⁵⁷ In the normal course of events, the original carbonyl group becomes reduced to a methylene group, and the terminal methyl of the alkyl group becomes oxidized to a thionamide structure (Eq. 93). With

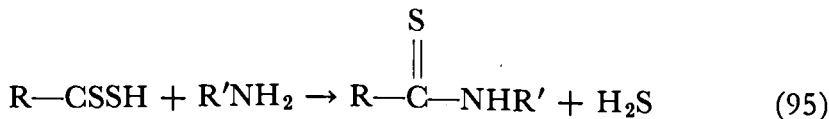


the use of ammonia, the reaction had to be carried out in sealed tubes, but the use of morpholine brings about the considerable improvement of allowing open equipment to be used. The reaction is successful with alkyl groups of various lengths, and it has been shown that the carbon skeleton does not undergo rearrangement. Initial attack is apparently oxidation by sulfur at the α -carbon, probably forming an α,β -double bond, which could migrate down the alkyl chain by successive additions and eliminations of amine or hydrogen sulfide. Further oxidation of the terminal methylene to a thionamide, and reduction of the carbonyl group, must obviously occur, but the exact steps are obscure. Benzaldehydes give thionbenzamides (Eq. 94). A similar effect can be obtained

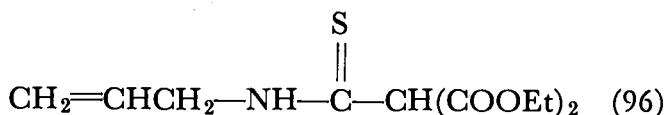


by oxidizing benzaldimines with sulfur (see Chapter 7).

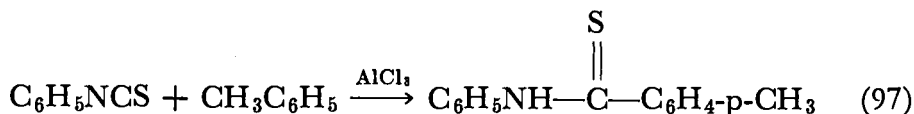
Direct thioacylation of ammonia and amines is possible with either dithio acids or their esters, and with thion esters ($\text{R}-\text{CS}-\text{OR}$) (Eq. 95); such reactions constitute a valuable synthetic method.



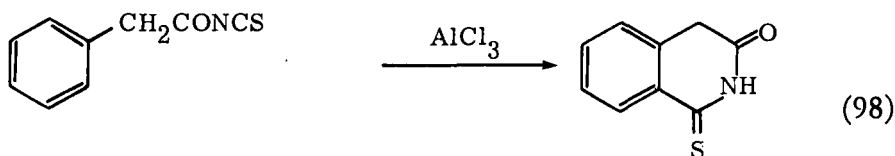
Substituted thionamides can be made from isothiocyanates either by reaction with organometallic reagents,^{52c} or by a Friedel-Crafts type of reaction with fairly reactive aromatic compounds.^{54d} Not only Grignard reagents, but also organolithium compounds and even sodio derivatives of active methylene compounds add readily (Eq. 96), and a wide variety



of thionamides is available by this means. The acid-catalyzed reaction



is a convenient route to thionanilides (Eq. 97). When acyl isothiocyanates are used, monothio imides are formed^{54b} (Eq. 98).



E. Imidic Acid Derivatives (Imido Esters, Imido Halides, etc.)

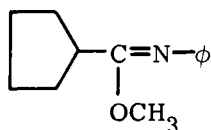
NOMENCLATURE AND GENERAL REMARKS Imidic acids have the general



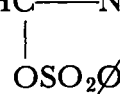
formula R—C(=NH)—OH , and are simply the enol tautomers of amides. Although evidence is now convincing that amides ordinarily have the keto structure, and all claims to have isolated separate imidic acid tautomers have been found to be false, the enol structure can be fixed by substitution. Numerous derivatives are known, and they form an important class of compound, of use primarily as intermediates in synthesis.

The principal types of derivatives are the esters, thio esters, halides, sulfonates, and phosphates. The esters are named by changing the name of the ordinary ester by substituting “-imidate” for “-ate,” and naming the N-substituent if there is one. Thus $\text{CH}_3\text{C(=NH)—OC}_2\text{H}_5$ is “ethyl N-

methylacetimidate,” $\text{C}_6\text{H}_5\text{C(=NH)—SCH}_3$ is “methyl thiolbenzimidate,” and


 is "methyl N-phenylcyclopentanecarbonimidate." The

other derivatives are named by use of the ordinary acyl derivative nomenclature, "-imidic acid" becoming "-imidoyl." Thus $\text{O}-\text{C}=\text{N}-\text{O}$ is


 "N-phenylbenzimidoyl chloride," and $\text{HC}=\text{NCH}_3$ is "N-methylform-


imidoyl benzenesulfonate." Such compounds as the latter are really mixed anhydrides, of course. The older, nonsystematic nomenclature is particularly horrible in the field of imidic acid derivatives, but since it has been widely used (and misused), it is necessary to be familiar with it. Usually either "imino" or "imido" was used as an uncertain infix, followed by "alkyl ether" or "chloride," as in "acetmethylimino-ethyl-ether" and "benzphenylimino chloride." A type of name derived from the principal method of formation of imidoyl chlorides, from amides, has also been used widely; according to it, N-phenylbenzimidoyl chloride is called "benzanilide imide chloride."

Imidate esters are known in which either the nitrogen or the oxygen is part of a ring, thus being related to lactams and lactones, respectively. Such heterocyclic compounds are not taken up in this book, but their chemistry is essentially that of the open-chain compounds, and their nomenclature is that of the corresponding heterocyclic systems.

PROPERTIES Imidate esters and imidoyl chlorides have low melting points, and most of the simple ones are liquids. They are much more volatile than the corresponding amides. Ethyl formimidate boils at 84° , and ethyl acetimidate at 90° ; N-methylbenzimidoyl chloride boils at 112° at 30 mm., corresponding to a boiling point at atmospheric pressure not far above 200° . The dipole moment of ethyl acetimidate, 1.33 D, is less than half that of acetamide. The vapors of both the esters and the chlorides are usually irritating to the eyes and nose.

Imidate esters are weak bases with values ⁵⁸ of pK_a from 7 to 9, thus standing between alkylamines and anilines (pK_a for $\text{CH}_3-\text{C}(=\text{NH}_2)^+-\text{OC}_2\text{H}_5$ is 7.6), and are in fact handled mostly as their salts. There is little difference in strength between thiolimidates and ordinary imidates. Imidoyl chlorides and other acyl derivatives are evidently much weaker bases, since they do not form hydrochlorides when they are prepared in anhydrous media by reactions that evolve hydrogen chloride. However,

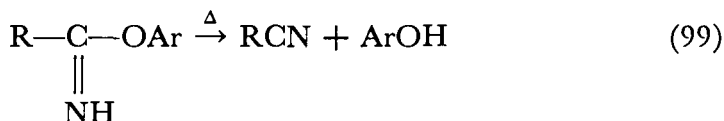
N,N-dialkyl immonium derivatives of both the esters and the chlorides are known, but only as salts, such as $(\text{CH}_3)_2\text{N}^+=\text{CHCl} \text{ Cl}^-$.

Imidoyl hexachloroantimonates, such as $\text{CH}_3\text{C}^+=\text{NCH}_3 \text{ SbCl}_6^-$, mp $178-181^\circ \text{ dec.}$, CN infrared stretch at 2416 cm.^{-1} , and perhaps imidoyl benzenesulfonates, are ionic substances, and are good conductors of electric current in solution in liquid sulfur dioxides.^{59a}

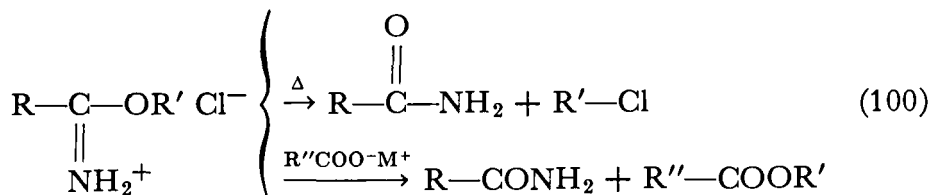
The smaller imidate esters are soluble in water, but hydrolyze fairly fast. Imidoyl chlorides, sulfonates, chloroantimonates, etc. are hydrolyzed by cold water so fast that their solubility has not been determined.

Imidoyl chlorides unsubstituted on nitrogen are not known unambiguously, and it appears that the compounds of corresponding formula that have been isolated are actually either salts or loose complexes of nitriles and hydrogen chloride^{59b,c} (see Chapter 5).

REACTIONS ^{18a} *Heat* The smaller alkyl imidates, even with unsubstituted nitrogen, are stable to distillation, but aryl imidates are split by the heat of distillation into nitriles and phenols (Eq. 99); thiol imidates



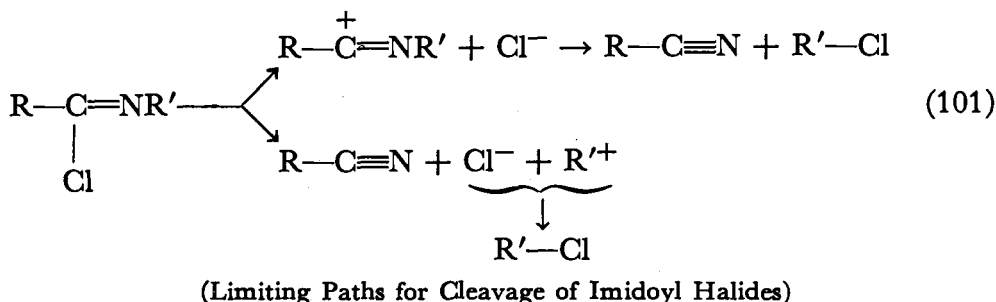
cleave even more easily. At temperatures above 250° , however, even alkyl imidates cleave to form nitriles. Alkyl imidate hydrochlorides are stable to storage, but mild to moderate heating (i.e., usually below 200°) causes most of them to decompose into alkyl halide and amide, in an $\text{S}_\text{N}2$ reaction that inverts the configuration of the alkyl group removed. The reaction is so easy that in some cases, treatment of an imidate ester with hydrogen chloride in ether is sufficient to cause cleavage.⁶⁰ Similarly,



carboxylate salts yield esters. As would be expected, alkyl groups, such as cyclohexyl, that are resistant to bimolecular displacement reactions give the corresponding olefin instead, and aryl groups are not displaced. The analogous reaction with alkyl thiolimidates, giving thionamides and alkyl halides, requires somewhat higher temperatures.

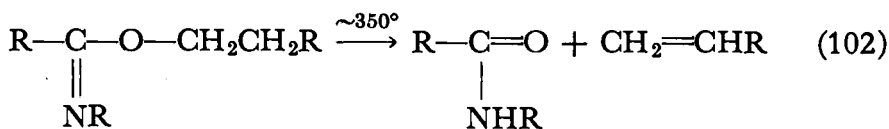
N-Alkyl imidoyl halides are easily decomposed by heat; nitriles are

formed and the N-substituents are removed as alkyl halides (usually) or olefins. In many cases, the temperatures required to produce imidoyl halides from the corresponding amide and such reagents as phosphorus pentachloride or thionyl chloride are sufficient to cause the following breakdown. Studies¹³ with various types of substituents have pointed to two limiting mechanisms for the breakdown: ionization of the halide followed by bimolecular displacement on the N-alkyl group by halide; and direct fragmentation into the nitrile, halide, and carbonium ion, followed by recombination of the latter two species (Eq. 101). The



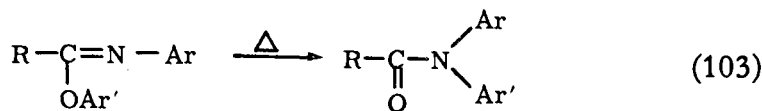
fragmentation path is favored by groups such as benzyl that form carbonium ions readily, and can be expected to result in racemization when an asymmetric carbon is cleaved from the nitrogen.

Strong heating of alkyl imidates brings about two competing reactions: elimination of olefin with formation of an amide (Eq. 102) and Chapman



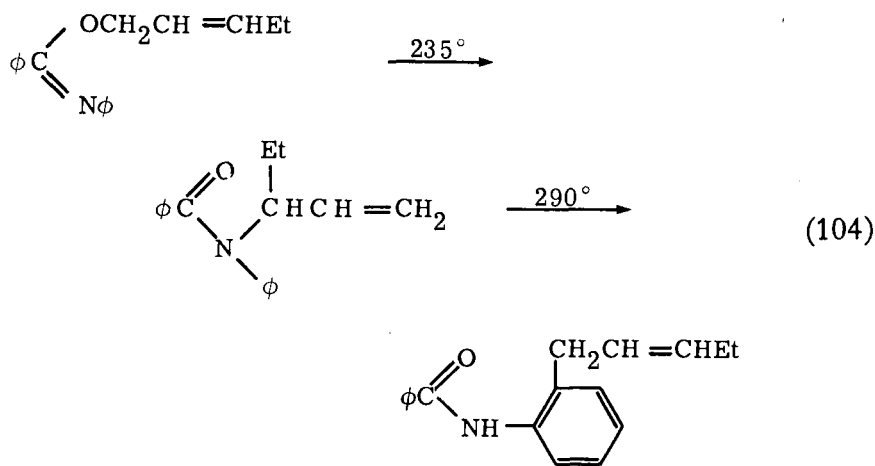
rearrangement. Elimination of olefin from imidate esters occurs at much lower temperatures than from the isomeric amide.⁶¹

In the Chapman rearrangement, the isomeric amide is formed, the O-alkyl group migrating to nitrogen (Eq. 103). Aryl imidates rearrange at lower temperatures and in better yield, and electron-withdrawing substituents on the migrating group accelerate the rearrangement so much



that picryl imidates rearrange rapidly even at room temperature. The migration has been shown to be a unimolecular internal process, and pairs of aryl imidates can be rearranged in the same solution without the formation of exchange products. Thiol imidates appear resistant to this rear-

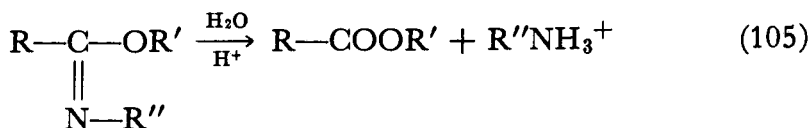
rearrangement. The migration of aryl groups in the Chapman rearrangement occurs without position isomerization (i.e., a *para* substituted group remains *para*), but allylic groups are isomerized. This is apparently a case of a four-membered-ring transition state being replaced by a six-membered-ring one, more favorable energetically, when the structure allows. With N-phenyl imidate esters, migration to the *ortho* position on the phenyl group may take place following or instead of migration to nitrogen ⁶² (Eq. 104). O-Acyl imidates (i.e., mixed acyl imidoyl anhy-



drides) also rearrange similarly, often very rapidly. Rearrangement of alkyl imidates is also reported to be catalyzed by small amounts of alkyl halides or iodine.

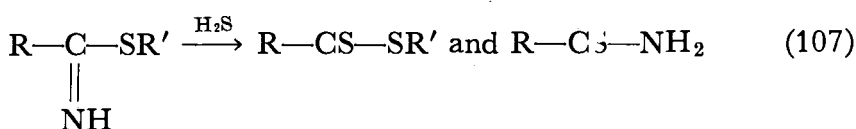
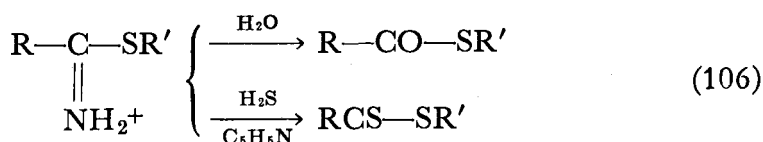
Solvolysis Solvolysis reactions form a very important part of the chemistry of imidic acid derivatives. Reactions occur quite easily, and can be accomplished not only with water, but with hydrogen sulfide, alcohols, mercaptans, and amines. All of the reactions are those to be expected from addition of a nucleophile to the tricoördinate carbon, followed by elimination, and are acid-catalyzed, although such catalysis is not always necessary.

Imidate esters hydrolyze very readily in the presence of dilute acid, and water solutions of their salts soon decompose into an ester and an amine salt (Eq. 105); the other possible path of hydrolysis, giving amides



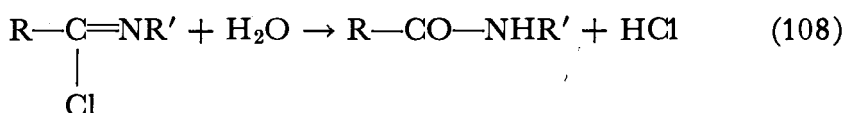
instead of esters, sometimes competes to a minor extent.⁶³ Hydrolysis is much faster than that of amides, and salts of imidate esters must be protected from atmospheric moisture in storage.

Thiol imidate esters give thiol esters by this reaction, and dithio esters by the analogous reaction with hydrogen sulfide (Eqs. 106, 107). Thion

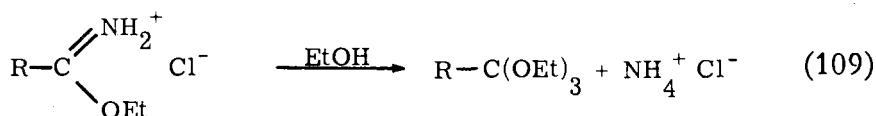


esters can be obtained from solvolysis of imidate esters with hydrogen sulfide, but the reaction is accompanied by a competing process in which alcohol is eliminated instead of ammonia, forming thionamides. Aqueous alkali catalyzes elimination with imidate esters having unsubstituted nitrogen, and they are converted to nitriles and alcohols.

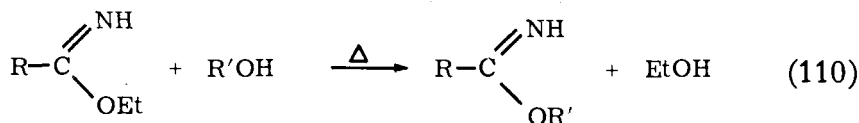
Imidoyl chlorides and analogous derivatives react with water to give amides essentially quantitative (Eq. 108).



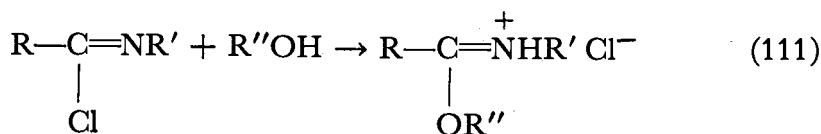
Alcoholysis of imidate ester salts occurs slowly at room temperature, and usually gives ortho esters,⁶³ for which the reaction is a useful synthesis (Eq. 109). It is not in general practical to accelerate the reaction by



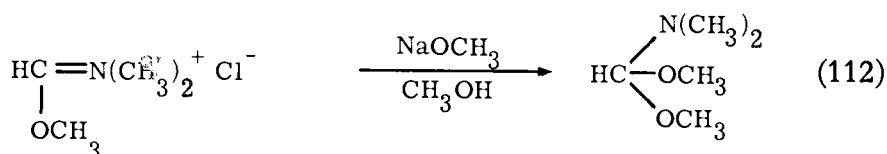
heating, because of the ease with which the cleavage giving alkyl halide and amide occurs. Alcoholysis of imidate esters as the free bases shows a quite different behavior, accomplishing alkoxy exchange instead (Eq. 110). Imidoyl chlorides react with alcohols to replace the chloride by



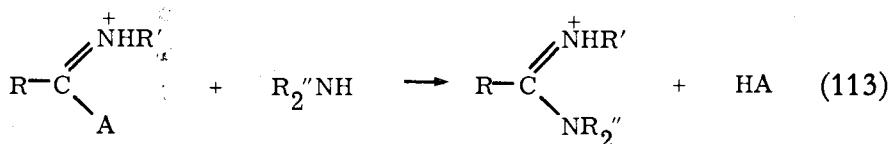
alkoxy, giving imidate ester salts (Eq. 111). Since further alcoholysis



to ortho ester occurs easily when acid is present, it is customary to use a base, such as a sodium alkoxide, when an imidate ester is wanted. Immonium derivatives of imidate esters undergo the first step of addition to the tricoördinate carbon, but elimination cannot follow, and "amide acetals" are produced (Eq. 112).



Aminolysis of either imidate esters or other imidoyl derivatives occurs easily near room temperature; ammonia, primary amines, or secondary amines can be used. The usual reaction produces amidines (Eq. 113);

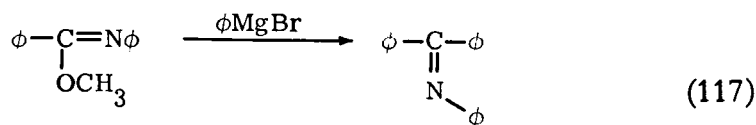


the alternative is amine exchange, leading to a differently substituted imidate ester. This appears to have been encountered only with α -amino acid derivatives and a few similar cases where a more weakly basic amine replaces a stronger one in the imidate ester.

Amidine formation takes place in both acidic and basic solution, but the details of the mechanism are different⁶⁴; amine exchange to a new imidate ester takes place only in neutral or acid solution. In every case an intermediate with tetrahedral carbon is formed by addition of the amine to the protonated imidate ester. In weakly basic solution, this intermediate eliminates alcohol as fast as it is formed, producing an amidine, but on the acid side, such elimination is much slower, and an amine may be eliminated instead. If the original amine bears different substituents from that on the imidate nitrogen, a mixture of two imidate esters can result from the intermediate. Eventually, however, all of the imidate ester(s) is converted to amidine, but owing to the imidate ester interchange, more than one amidine may be formed (Eq. 114). Imidoyl chlorides have not been observed to show these exchange reactions, presumably because simple ionization of the C—Cl bond in the intermediate, resulting directly in a stable amidinium salt, is much faster than amine elimination.

The foregoing solvolysis reactions can be carried out in various combinations using bifunctional compounds, such as mercapto amines, amino alcohols, etc. When the two functions are separated by two or three carbons, ring closure occurs readily, and a rich variety of heterocyclic

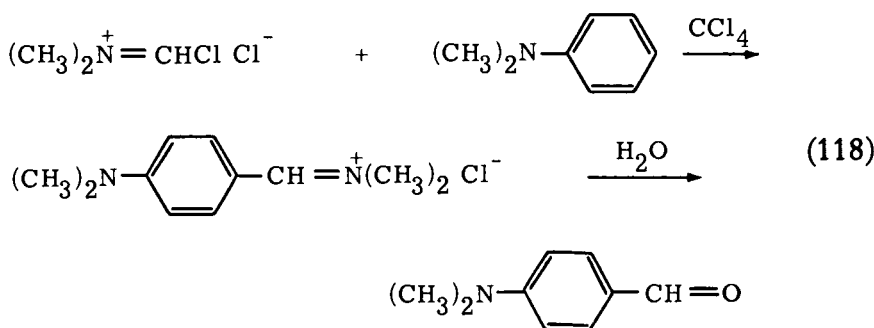
Grignard reagents will add to imide esters, whether the nitrogen is substituted or not, analogously to their reaction with ordinary esters.⁶⁵ Alkoxide is eliminated, and ketimines (or aldimines in the case of formimides) are produced; the reaction does not ordinarily continue with a second equivalent of Grignard reagent, owing to the relative sluggishness of ketimines toward organometallic reagents (see Chapter 7) (Eq. 117).



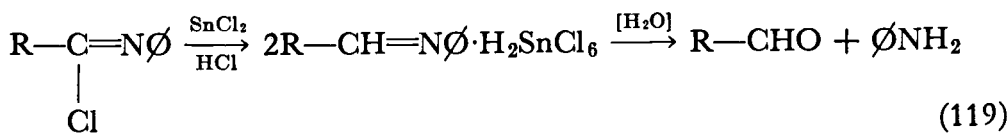
(Grignard reaction with imide esters)

Other carbanion sources react similarly, so that all "active methylene" compounds, as exemplified by malonic ester, can be expected to condense with imide esters. For both steric and electronic reasons, formimides are the most reactive.

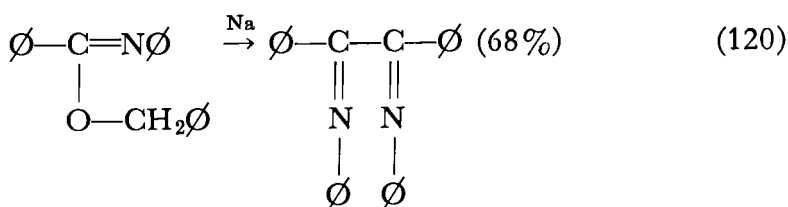
The Vilsmeier-Haack reaction, in which an amide is made to condense with a reactive aromatic ring under the influence of phosphoryl chloride and similar reagents, is apparently actually a reaction of intermediate imidic acid derivatives (see Part A, "Amides"). Dimethylformamide, for example, can be converted to an immonium salt, which will then react with dimethylaniline in the absence of a catalyst to produce *p*-dimethylaminobenzaldehyde (Eq. 118).



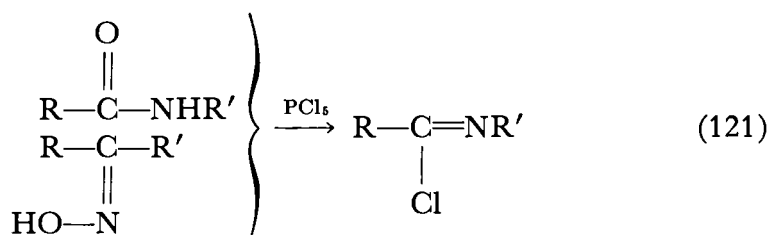
Reduction of imidoyl chlorides can be accomplished with anhydrous stannous chloride; the products are aldimine chlorostannates, which are easily hydrolyzed to aldehydes (Eq. 119). Since imidoyl chlorides are



easily made from carboxylic acids through their anilides, the over-all process is a useful aldehyde synthesis; it is called the Sonn-Müller reduction.^{66a} Sodium reduces imide esters to diimines of α -diketones^{66b} (Eq. 120).

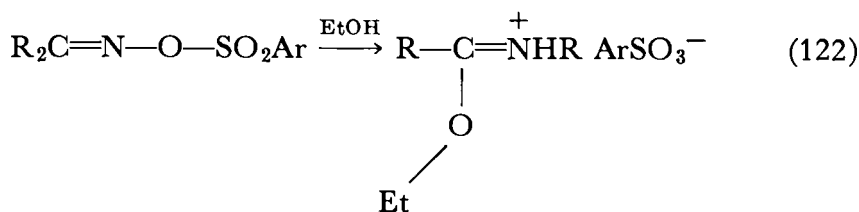


PREPARATION ^{18a} The preparation of imidoyl chlorides by the reaction of phosphorus pentachloride or similar reagents with amides has been mentioned in connection with reactions of amides. This reaction and the Beckmann rearrangement of oximes, brought about by the same reagent, constitute the only significant synthetic methods (Eq. 121).

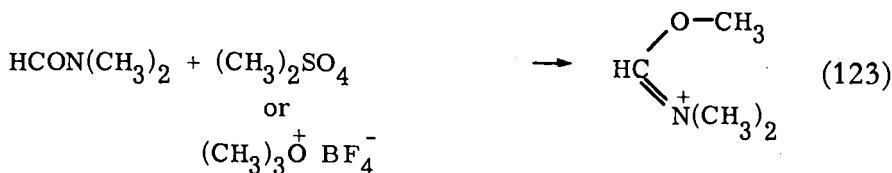


Other imidoyl derivatives can be prepared by similar reactions, such as the action of benzenesulfonyl chloride on amides or oximes; in such cases, the imidoyl benzenesulfonates or related compounds are primarily of significance only as reaction intermediates prepared *in situ*, for they rearrange very readily.

Imidate esters substituted on the nitrogen can be prepared from the foregoing imidoyl derivatives, either by alcoholysis or reaction with sodium alkoxides. The Beckmann rearrangement of O-benzenesulfonyl oximes in the presence of alcohol thus gives imidate esters (Eq. 122). An

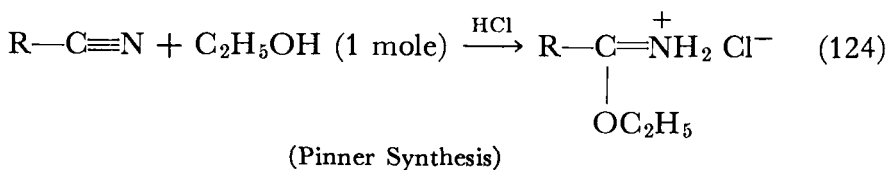


alternative that has not been as widely used is the alkylation of amides or their silver salts. Alkylation of amides with alkyl halides is a difficult reaction, but sulfates or oxonium salts work well ^{18d} (see Part A, "Amides") (Eq. 123). Thionamides are alkylated considerably more easily, even by

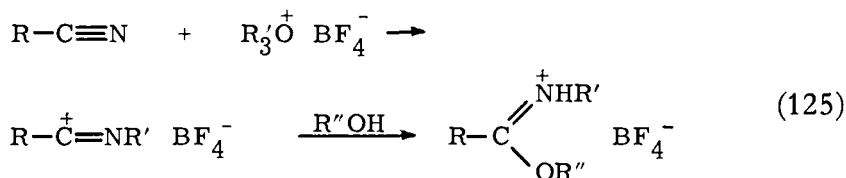


alkyl halides, to give thiol imidates. Alkylation is the only method with the multiple capability of producing imidates with two, one, or no substituents on the nitrogen.

The classical Pinner synthesis of imidate esters utilizes the addition of alcohols or mercaptans to nitriles under catalysis by hydrogen chloride; it can obviously produce only unsubstituted products (Eq. 124). It has



recently been found that the same result can be obtained with traces of base as catalyst, but this only works well when there are electron-withdrawing substituents on the nitrile.⁶⁷ Nitriles can also be converted to imidate esters by a modification of the Ritter reaction due to Meerwein and his students.³⁷ The nitrilium salts obtained by the alkylation of nitriles with trialkyloxonium salts are converted to imidate esters at once on exposure to alcohols (Eq. 125). N-Arylformimidate esters are avail-



able from the reaction of alkyl orthoformates with aromatic amines.⁶⁸

F. Amidines

NOMENCLATURE AND GENERAL REMARKS Amidines are the completely ammonolyzed analogues of carboxylic acids, corresponding to isoelectronic replacement of =O by =NH, and —OH by —NH₂. They are named on the basis of the names of the corresponding acids, the “-ic” ending being replaced by “-amidine,” sometimes with the elision of an “o”; names ending in “-carboxylic acid” are changed to end in “-carboxamidine.” Thus we have “acetamidine” for CH₃C(=NH)NH₂, “benzamidine” for $\text{C}_6\text{H}_5\text{C}(=\text{NH})\text{NH}_2$, and “dodecane-1,12-dicarboxamidine” for H₂N—C(=NH)(CH₂)₁₂C(=NH)NH₂. Substituents on the nitrogens are named in the ordinary manner, using *N*- and *N'*- as the locants, as in “*N*-methyl-*N'*-phenylpropionamidine,” CH₃CH₂C(=N $\emptyset$)NHCH₃. The problem of distinguishing between the double-bonded and the single-bonded nitrogen has not arisen, since separate tautomeric forms of noncyclic amidines have never been isolated. The group —C(=NH)NH₂ treated as a substituent is sometimes called

“guanyl.” Compounds with the structure $RC(=NR)NHC(=NH)R$ are called imidines.

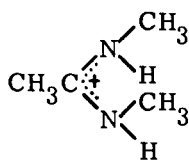
The amidine structure is important in nature in cyclic derivatives: the imidazoles (called glyoxalines in England), and the pyrimidines, which are structural features of certain enzymes and all purines.

PROPERTIES All unsubstituted amidines appear to be solids, but few of the smaller ones have been isolated in pure form, owing to their high water solubility, hygroscopic character, and sensitivity to hydrolysis. Benzamidine melts at $75-80^\circ$, its N-methyl, N,N-dimethyl, and N,N,N'-trimethyl derivatives are oils, and N,N'-dimethylbenzamidine forms a hemihydrate that melts at 81° .

Amidines are among the strongest organic bases⁶⁹ outside of the quaternary ammonium hydroxides. Acetamidine, pK_a 12.4, and benzamidine, pK_a 11.6, are far stronger than any aliphatic amine. Aryl and acyl substitution understandably reduces the basicity, but such derivatives are still capable of forming salts with dilute aqueous acids. N,N'-Diphenylacetamidine, pK_a 8.3, is still quite basic, and N,N-diphenylbenzamidine, which is not precipitated from solutions of its salts by ammonia, may be slightly stronger than its isomer. Most amidines readily form salts with weak acids, such as carbonates and nitrites. Amidines having at least one N—H are also very weakly acidic, and will form metal salts when treated with alkali metal amides in liquid ammonia. Some N,N'-diarylformamidines are slightly more acidic than water.^{69c}

The amidine structure shows infrared absorption⁷⁰ similar to amides; two bands are usually found in the double-bond region, one at $1455-1607\text{ cm}^{-1}$, the other at $1620-1690\text{ cm}^{-1}$.

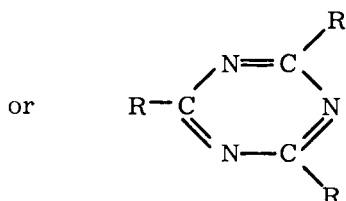
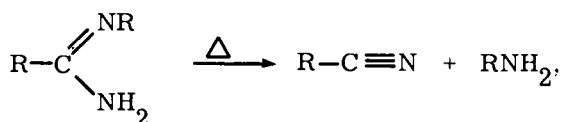
Tautomerism is clearly possible with monosubstituted amidines and disubstituted amidines bearing a different substituent on each nitrogen, but only in the case of certain imidazoles have pairs of tautomers actually been isolated. The cations of such tautomers are identical, owing to protonation at the imine nitrogen. N-Aryl amidines appear to exist preferentially as the arylimino tautomer, presumably owing to the conjugation then possible. Nmr spectra indicate a lack of free rotation about either RC—N bond in amidinium cations. As a result, substituents on the nitrogens have fixed orientations; the preferred configuration is evi-



(amphi configuration of an amidinium ion)

dently *amphi*, inasmuch as the N-methyl groups in N,N'-dimethylacetamidinium ion are nonequivalent.⁷¹

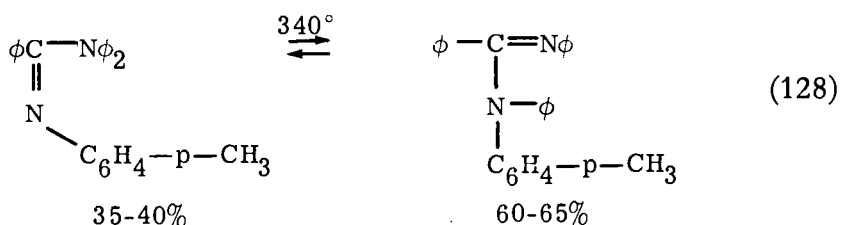
REACTIONS ⁷² Amidines in general are stable substances, but they decompose to nitriles and amines or polymerize to *sym*-triazines ^{73a} when strongly heated if one nitrogen is unsubstituted (Eq. 126). Alkali metal (126)



salts of amidines decompose on heating in the presence of sodium amide, in the isoelectronic analogue of decarboxylation ^{73b} (Eq. 127).



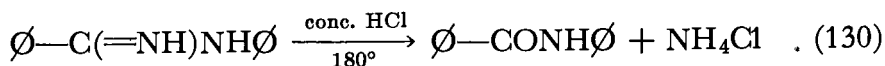
When both nitrogens are substituted, strong heating causes rearrangement ⁷⁴ analogous to the Chapman rearrangement of imidate esters. The reaction does not occur as easily, however, and comes to equilibrium with appreciable amounts of both isomers (Eq. 128); the migration of



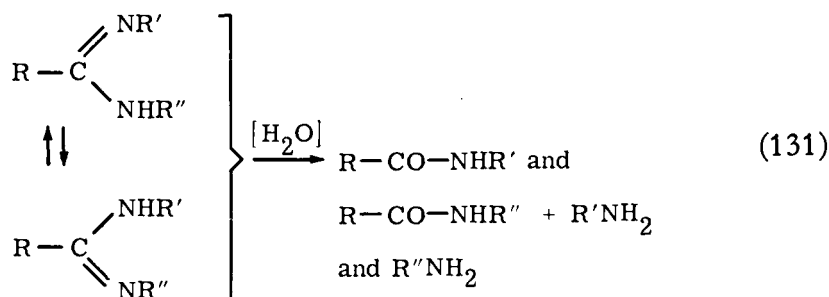
the aryl group is apparently intramolecular. Amidines are hydrolyzed far more easily than are amides, esters, or nitriles. Hydrolysis is catalyzed by both acid and base, but acetamidine is hydrolyzed by hot water alone (Eq. 129). Resistance to hydrolysis is greatly increased by substitution,



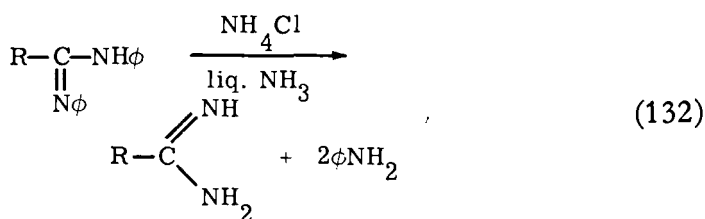
and partial hydrolysis to amides is usual (Eq. 130), whereas aryl substi-



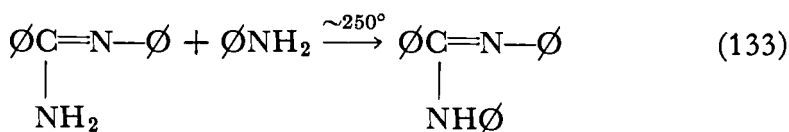
tution can make amidines quite difficult to hydrolyze.^{69c} When the nitrogens are differently substituted, partial hydrolysis often produces both amides (Eq. 131). Hydrogen sulfide reacts analogously with ami-



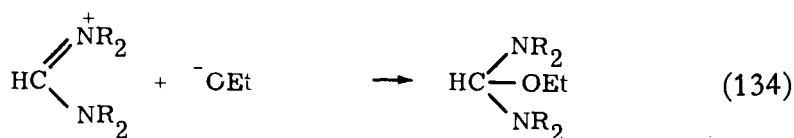
dines, producing thionamides; the reaction is usually carried out at 120–130°, and sealed tubes are thus required.⁷⁵ Aminolysis is brought about by liquid ammonia in the presence of ammonium chloride as acid catalyst (Eq. 132), or simply by heating an amidine with a primary amine (Eq.



133). Analogous reactions occur with hydrazines and hydroxylamine,

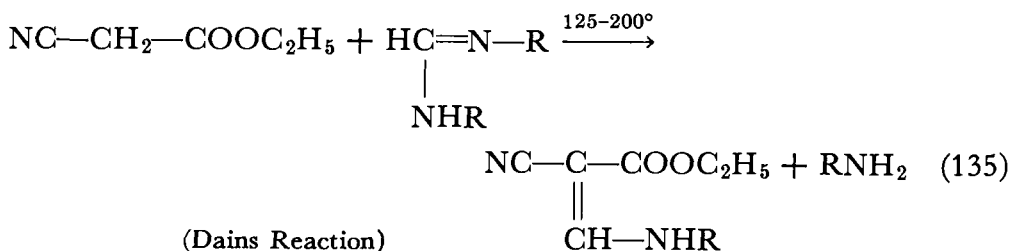


producing imidoyl hydrazides (amidrazones) and amidoximes.⁷⁶ All of these solvolysis reactions presumably occur by addition of the solvolysing nucleophile to the tricoördinate carbon of either the amidine or its cation, followed by elimination. When there are no hydrogens at all on the amidinium ion, elimination is obviously impossible; in such cases, the intermediate addition compounds, derivatives of ortho acids, can sometimes be isolated ⁷⁷ (Eq. 134).



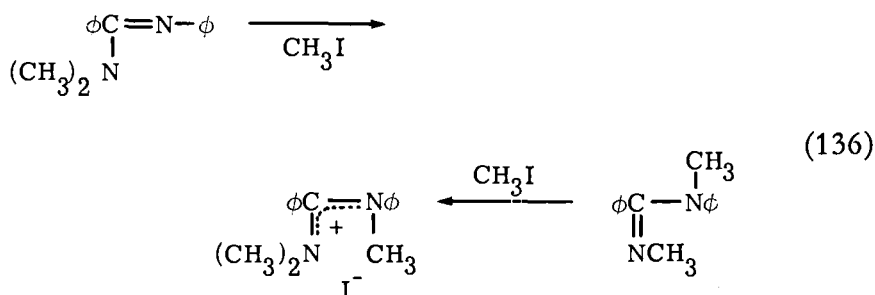
Formamidines act as acylating agents toward “active methylene” compounds, such as cyanoacetic ester and nitromethane, producing aldi-

mines or the tautomeric enamines (Eq. 135), in a reaction closely related

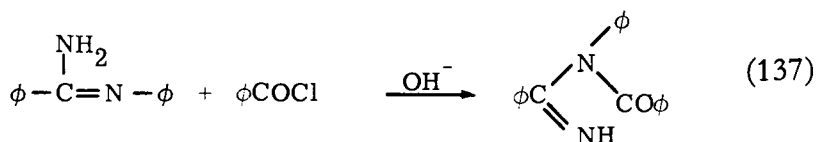


to the foregoing solvolyses. The basic amidines apparently act as their own catalysts. This is sometimes called the Dains reaction.⁷⁸

Essentially all amidines can be alkylated by alkyl halides, mild heating being usual, necessitating sealed tubes with the smaller alkyl halides. When the nitrogens are differently substituted, mixtures of products can be expected, but there is evidence that the alkylation actually takes place preferentially on the double-bonded nitrogen. N-Phenyl-N',N'-dimethyl-, and N-phenyl-N,N'-dimethyl-benzamidine react with methyl iodide to give the identical amidinium salt, for example ⁷⁹ (Eq. 136).



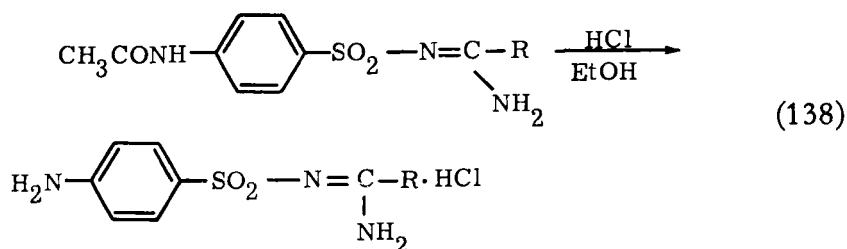
Acylation occurs easily under Schotten-Baumann conditions (Eq. 137);



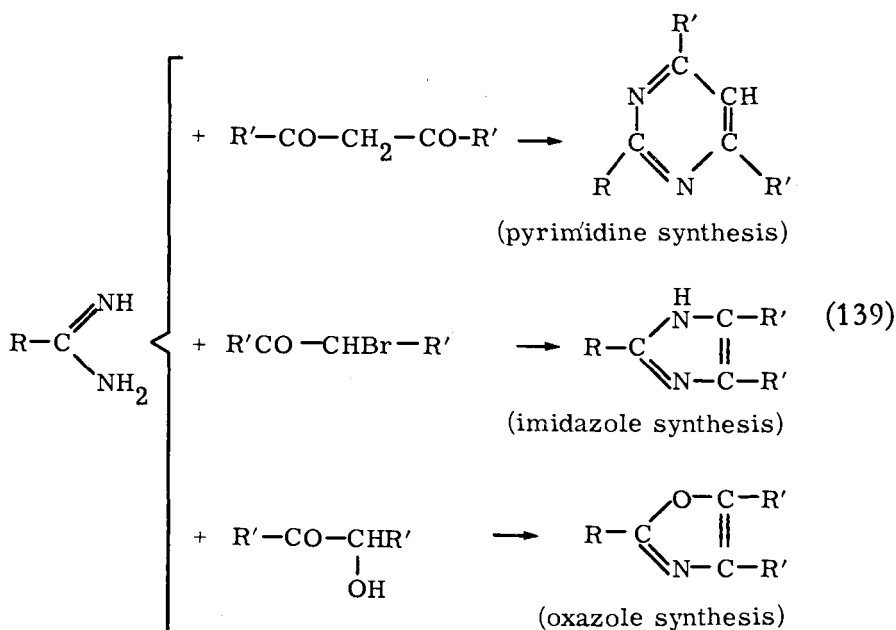
monoacylation is usual, but diacylation can be accomplished. The acylated amidines so formed are often surprisingly resistant to solvolysis, as shown by *p*-acetamidobenzenesulfonylamidines, in which the acetamido group can be alcoholized without disturbing the amidine system (Eq. 138).

Ionic halogenating agents, such as hypochlorous acid, convert unsubstituted amidines to N-monohalo derivatives. This occurs so readily that a quantitative volumetric determination of amidines has been based on the reaction with potassium triiodide solution.⁸⁰

Aldehydes and ketones, especially the former, react with the $-\text{NH}_2$

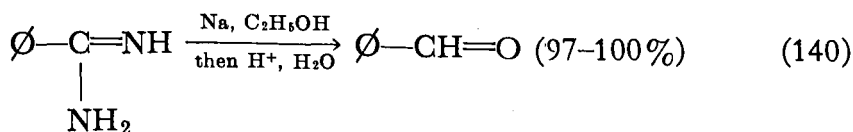


group of unsubstituted or monosubstituted amidines to form imidoyl imines. This reaction has its principal importance in combination with alkylation or acylation by bifunctional compounds. β -Dicarbonyl compounds and their relatives, for example, condense with both nitrogens of amidines, producing pyrimidines, and when the functions stand in 1,2-relation to each other, as in α -halo ketones, imidazoles are formed (Eq. 139). Both of these reactions are of great synthetic importance.⁸¹ Still



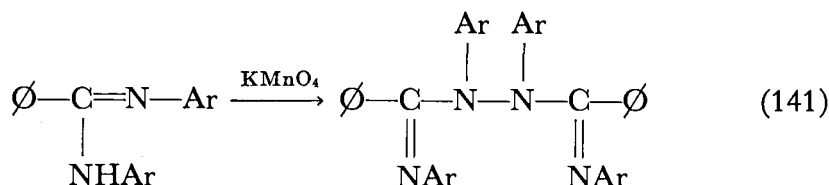
other heterocyclic systems can be prepared from amidines by reaction with bifunctional compounds that close a ring by a combination of solvolysis with substitution.

Reduction of amidines by sodium and alcohol, with or without liquid ammonia, converts them to aldimines, mostly in high yield.²⁶ Since these products are hydrolyzed almost effortlessly during work-up, the reaction is a valuable aldehyde synthesis (Eq. 140). Substituted amidines are reduced by sodium amalgam in acetic acid to secondary amines, a reaction

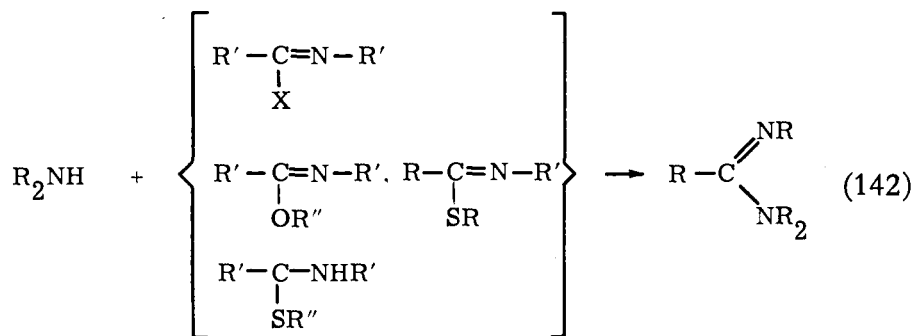


of primary value in structure proof. Amidines are for practical purposes inert to catalytic hydrogenation.

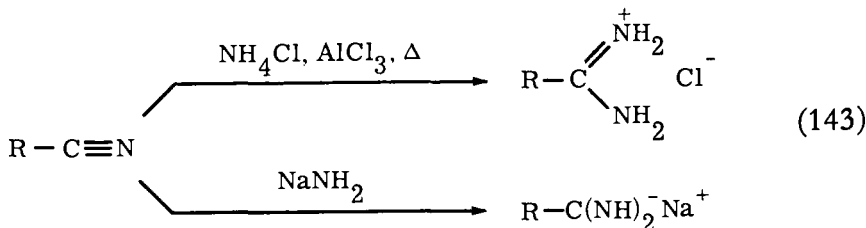
Oxidation of amidines usually attacks the N-alkyl substituents, but N,N'-diarylbenzamidines in general are attacked at the nitrogens by permanganate, producing hydrazine derivatives ⁸² (Eq. 141).



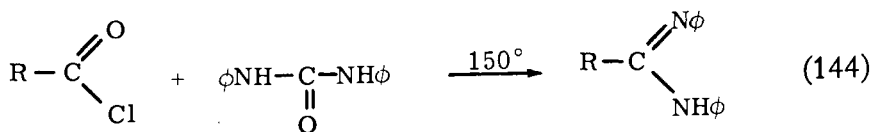
PREPARATION Many of the preparative methods for amidines have already been mentioned in connection with the chemistry of thionamides and imidic acid derivatives. The solvolysis of thionamides, imidoyl halides, sulfonates, chlorophosphonates, etc., and imidate ⁶⁴, ^{67a} and thioimide esters with ammonia or amines is probably the most important group of syntheses for amidines (Eq. 142). Through such intermediates,



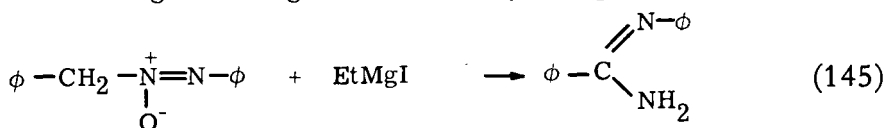
even without isolation, amides can be converted to amidines; phosphorus halides are the usual condensing agents.⁸³ A more limited method is the addition of ammonia or amines to nitriles, which can be brought about both by acid catalysis ^{84a,b} (heating with ammonia and ammonium salts under pressure) and base catalysis ^{84c} (sodium amide) (Eq. 143).



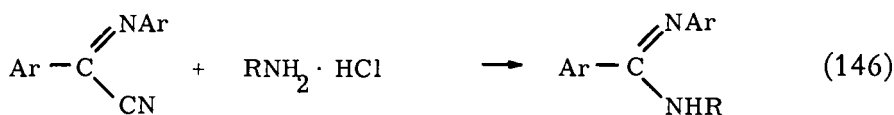
The Dains synthesis (Eq. 144), by which amidines are produced from acid



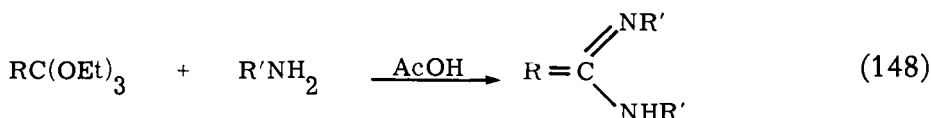
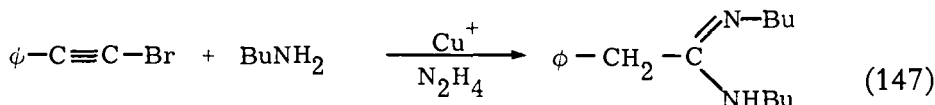
chlorides and ureas, is described in Chapter 6. In addition to these methods, many other reactions, such as the pyrolysis of amides ⁶ and of imidate esters, and the base-catalyzed rearrangement of hydrazones, ⁸⁵ give variable quantities of amidines. Among these may be mentioned the reaction of Grignard reagents with azoxy compounds ⁸⁶ (Eq. 145),



the oxidation of aldimines (Chapter 7), the reaction of enamines with azides (Chapter 7), the cleavage of α -imino nitriles with amine salts ^{87a} (Eq. 146), and the solvolysis of bromoacetylenes, ^{87b} ortho esters or thio



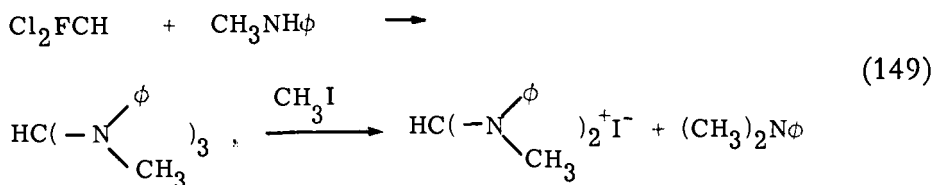
ortho esters with amines ^{87c} (Eqs. 147, 148). The last reactions ⁸⁷ have

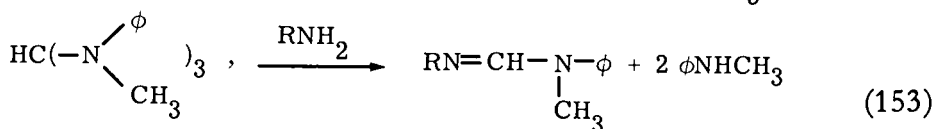
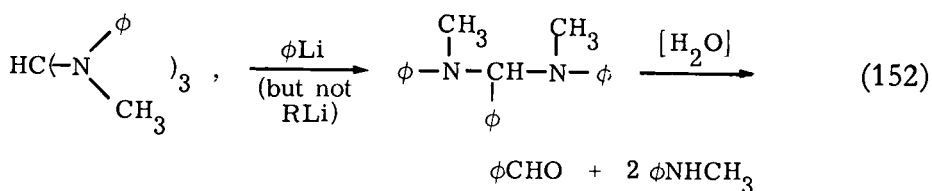
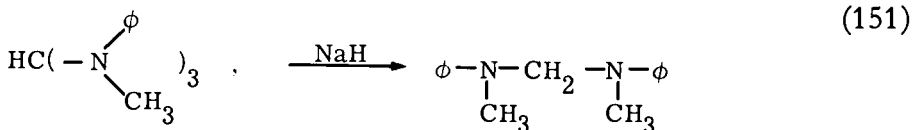
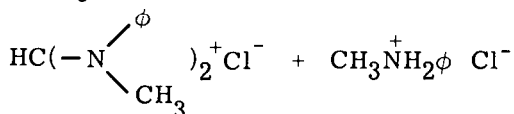
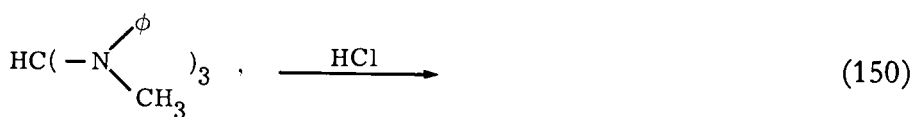


only recently been advanced as preparative methods, but appear to be of considerable utility.

G. Orthoamides

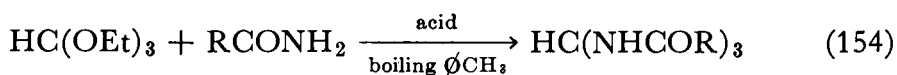
Substances of the type $\text{RC}(\text{NR}_2)_3$ are known as ortho amides, in analogy with ortho esters, $\text{RC}(\text{OR})_3$. Individual members are most conveniently named as 1,1,1-triaminoalkanes. Relatively little is known about these compounds. *Tris*-(N-methylanilino)methane is formed from the sodium derivative of N-methylaniline and dichlorofluoromethane ⁸⁸ (Eq. 149). It is a high-melting, insoluble substance, whose characteristic behavior towards most reagents is to expel one of the amino





(Representative Reactions of an Orthoamide)

groups to form an amidine (Eqs. 150–153). *Tris*-(acylamido)methanes, formed by the action of methyl sulfate on formamide, as well as from orthoformates and amides (Eq. 154), have recently been shown to be a



valuable intermediates for pyrimidine syntheses.⁸⁹

Ortho amides are also formed by the reaction of completely substituted formamidinium salts with sodium hydride and *N*-methylaniline, by the reaction of sodium trichloroacetate with *N*-methylaniline, and to a small extent when *N*-methylaniline and ethyl orthoformate are refluxed for a month.⁸⁸ The reported preparation of an orthoacetamide from the reaction of ketene acetal with piperidine has been shown⁹⁰ to give a vinylidenediamine instead, and the reported preparation of the same ortho amide from 1,1,1-trichloroethane and piperidine has been shown to give ethylenedipiperidine. Ortho ester amides, $\text{RC}(\text{OR})_2\text{NR}_2$, called amide acetals, are stable, weak bases.⁹¹ They are prepared by treating *N,N*-dialkyl imidate ester salts, $\text{RC}(\text{OR})\text{NR}_2^+\text{X}^-$, with sodium alkoxides, and have special value for converting carboxylic acids into their esters.

AMIDES OF THE SULFUR ACIDS

NOMENCLATURE AND GENERAL REMARKS In this part, the lion's share of attention will be accorded the sulfonamides, for their present importance is far greater than that of the other classes.

Sulfonamides are named quite simply in the same manner as carboxamides, by changing the terminal "-ic" of the name of the parent acid to "-amide," and indicating substituents on the nitrogen by the locant "N-". It should be borne in mind that sulfonic acids are named by the additive method, and their names are thus derived from that of the hydrocarbon, *not* the corresponding radical. The compound $C_6H_5-SO_2NHCH_3$ is correctly named "N-methylbenzenesulfonamide." Sulfonimidyl amides,

$$\begin{array}{c} O \\ || \\ R-S-NH_2 \\ || \\ NH \end{array}$$
 are the sulfonic acid analogues of amidines. Sulfonamides

do not have significant natural occurrence, but they are very important as drugs, intermediates in synthesis, and derivatives for isolation and identification. Although for convenience most organic chemists express the sulfonyl group as simply " RSO_2 ", it is pertinent to consider the nature of the S—O bonding. Evidence has accumulated⁹² that it is a true double bond, involving the *d*-orbitals of sulfur, although the conclusion is not yet unequivocal.

Sulfamides, $R_2NSO_2NR_2$, are named as substituted derivatives of sulfamide, $H_2NSO_2NH_2$, by specifying the substituents in the usual way. The half-amides of sulfuric acid, R_2NSO_3H , are named as substituted sulfamic acids.

The amides of sulfurous acid are represented principally by the thionyl amines, which give the structure exemplified by thionylaniline, $\phi-N=S=O$. The same oxidation state of sulfur is found in the sulfin-

$$\begin{array}{c} O \\ || \\ R-S-NR'_2 \end{array}$$
 amides, $R-S-NR'_2$. Compounds with the structure $R-S-NR'_2$, derived from the sulfenic acids, $R-SOH$, are known as sulfenamides, and also as hydrosulfamines and "isothiamides"; they are discussed along with hydroxylamine derivatives (Chapter 8).

PROPERTIES Unsubstituted sulfonamides are all solids, and the smaller ones are readily soluble in water. Alkyl substitution lowers the melting point, just as it does with carboxamides. The melting points generally lie a little above those of the corresponding carboxamides. Boiling points are quite high, as shown by N-methylethanesulfonamide,

bp 276°. Tetramethylsulfamide, $\text{Me}_2\text{NSO}_2\text{NMe}_2$, an organic amide of sulfuric acid, melts at 73° and sublimes readily. Dimethylsulfamic acid, mp 165°, and phenylsulfamic acid, mp > 280°, are strong acids easily soluble in water. Their melting points and solubility strongly suggest that they exist primarily as zwitterions, as is necessarily the case with

trisubstituted derivatives, $\text{R}_3\text{N}^+\text{—SO}_3^-$ (amine-sulfur trioxide adducts).

Sulfonamides bearing no more than one substituent are acidic, with a strength similar to phenols. This effect of sulfonyl substitution is thus greater by about six powers of ten than the effect of acetyl substitution, and sulfonamides are stronger than carboxamides to about the same extent as sulfuric acid is stronger than acetic. Sulfonamides are thus usually soluble in aqueous sodium hydroxide, but not in sodium carbonate solutions. The basicity of sulfonamides must be extremely low, as it is not ordinarily apparent, but the phenomenon of acid catalysis of hydrolysis of sulfonamides indicates that there is indeed some basicity.

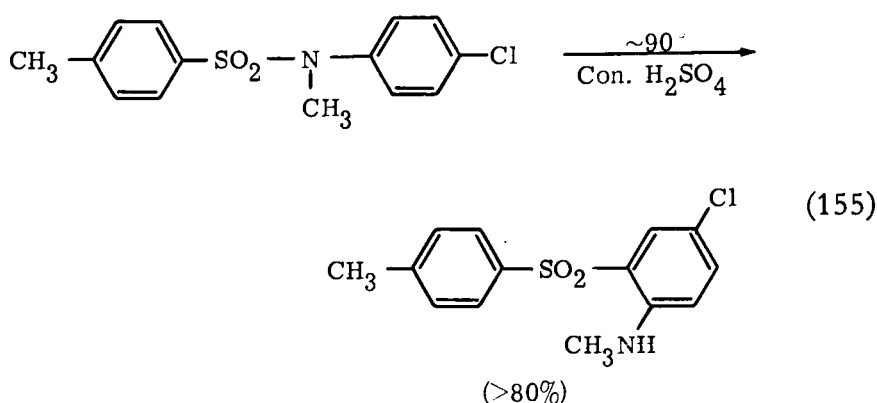
Thionyl amines are neutral, easily hydrolyzed substances. Methylthionylamine, $\text{CH}_3\text{N}=\text{S}=\text{O}$, has mp 58–59°, and thionylaniline is an oil, bp 200°; tetramethylthionylamide, $(\text{Me}_2\text{N})_2\text{SO}$, is an oil, bp 69°/8 mm. Sulfinamides are little known; benzenesulfinamide, $\text{C}_6\text{H}_5\text{SONH}_2$, colorless crystals, mp 121°, is slightly soluble in water, and N,N-dimethylbenzenesulfinamide is a yellow oil, noticeably soluble in dilute acids,⁹³ whereas dimethylaminesulfinic acid, $(\text{CH}_3)_2\text{NSO}_2\text{H}$, has been reported as a yellow, crystalline mass.

REACTIONS⁹⁴ Sulfonamides are for the most part unusually stable to heat, but in the presence of some acid, sulfonanilides occasionally rearrange on heating to form aminophenyl sulfones (Eq. 155). A similar reaction has been observed with diphenylsulfamide, $\text{C}_6\text{H}_5\text{NHSO}_2\text{NHC}_6\text{H}_5$. This rearrangement is obviously related to the rearrangement of N-nitroso and N-nitro anilines to the ring-substituted isomers. It appears to be an intermolecular rearrangement, on the basis of the observation that when diphenylsulfamide is heated in the presence of

Table 4-3

Melting points of some sulfonamides

$\text{CH}_3\text{SO}_2\text{NH}_2$	88°
$\text{C}_2\text{H}_5\text{SO}_2\text{NH}_2$	60°
$\text{C}_2\text{H}_5\text{SO}_2\text{NHCH}_3$	3–7°
$\text{C}_2\text{H}_5\text{SO}_2\text{N}(\text{CH}_3)_2$	oil
$\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2$	156°
$\text{C}_6\text{H}_5\text{SO}_2\text{NHCH}_3$	31°
$\text{C}_6\text{H}_5\text{SO}_2\text{N}(\text{CH}_3)_2$	48°
$p\text{—CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2$	137°

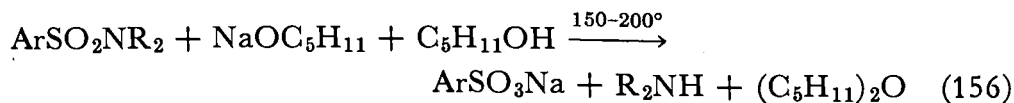


dimethylaniline, the migrating sulfonyl group is intercepted, forming *p*-dimethylaminobenzenesulfonanilide.⁹⁵

Salt formation with strong bases is a natural consequence of the acidity of sulfonamides bearing not more than one N-substituent, but not every such sulfonamide will dissolve in aqueous alkali. Some form relatively insoluble sodium salts, and others are too feebly basic, facts that limit the reliability of the classical Hinsberg method for distinguishing among and separating primary, secondary, and tertiary amines (see Chapter 2). The use of methanol solutions of alkali removes some of the difficulties.

Hydrolysis of sulfonamides⁹⁶ is extremely slow compared to carboxamides, and usually requires conditions that are somewhat drastic. Unsubstituted and monosubstituted sulfonamides in many cases withstand fusion with 80% sodium hydroxide at 250°, a situation to a considerable extent due to the formation of the sulfonamide anion; the presence of a negative charge would repel the approach of the hydroxide ion necessary for hydrolytic cleavage. Although *p*-nitrobenzenesulfonamides are somewhat more easily hydrolyzed by base, the reaction is still not regarded as a useful one. Acid-catalyzed hydrolysis is also difficult, and even heating with concentrated hydrochloric acid at 150–170° in a sealed tube, commonly used conditions, sometimes fails, although refluxing overnight with 25% hydrochloric acid is successful in many cases. Lewis acids, such as zinc or aluminum chloride, accelerate the process. Sulfuric acid can be used for hydrolysis, but it may also catalyze the rearrangement to sulfones, and may sulfonate susceptible aryl groups. Solvolysis with hot acetic acid containing strong mineral acids often works well.

Base-catalyzed alcoholysis can be accomplished with disubstituted sulfonamides if a sufficiently high temperature is used. The most successful reagent seems to be sodium isoamyloxide in isoamyl alcohol (3-methylbutanol) at 150–200° (Eq. 156). Since this reaction fails with mono-



substituted sulfonamides, owing to formation of a resistant anion, it has been proposed as a supplementary method in the Hinsberg separation of primary and secondary amines. The reaction very probably involves attack by RO^- on sulfur, which becomes pentacoöordinate in the transition state. The initial product must be a sulfonate ester, which is converted to an ether and sodium salt by reaction with a second alkoxide ion.

Aminolysis of sulfonamides can be brought about at about 200° under acid catalysis by amine salts, and in many cases by amines alone, although the reactions are difficult. Sodium amides bring about aminolysis of disubstituted sulfonamides more easily⁹⁷ (Eq. 157). Trisulfonamides,

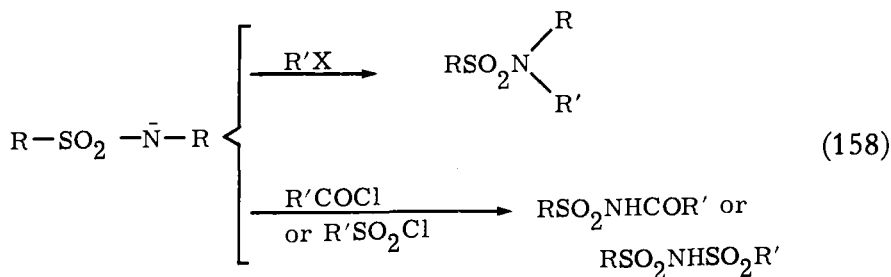


$(\text{RSO}_2)_3\text{N}$, are much more susceptible to nucleophiles, and sodium ethoxide or piperidine will cleave them to disulfonamides in less than an hour on a steam bath.

Sulfamides are cleaved by nucleophilic reagents similarly to sulfonamides. The kinetics suggest that with some N-aryl sulfamides, base-catalyzed dissociation to sulfimide, $\text{HN}=\text{SO}_2$, occurs.⁹⁸ Alkyl sulfamic acids are slowly hydrolyzed by boiling water in the presence of acid or base, but arylsulfamic acids are hydrolyzed much more rapidly.⁹⁹

Sulfinamides are decomposed when hydrolysis is attempted with aqueous acids, but they are smoothly cleaved by alkali.⁹³ Thionylamines, however, are much more sensitive, and are hydrolyzed even by cold water.

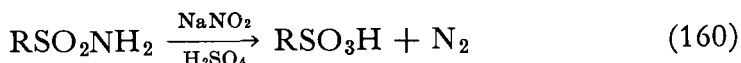
Sulfonamides bearing not more than one substituent can be either alkylated or acylated in the form of their sodium salts (Eq. 158). The use



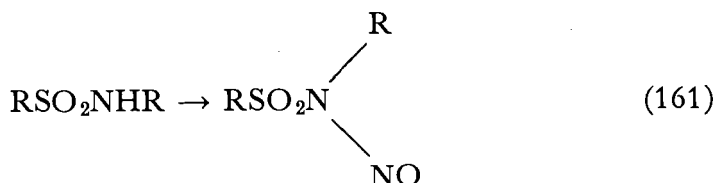
of such reactions in the preparation of secondary amines has been mentioned in Chapter 2. With suitably chosen quantities, dialkylation and diacylation can be accomplished. With disubstituted sulfonamides and under other conditions, acyl exchange can take place, as in the conversion of N,N-dimethylethanesulfonamide to dimethylnitramide^{100a} (Eq. 159).



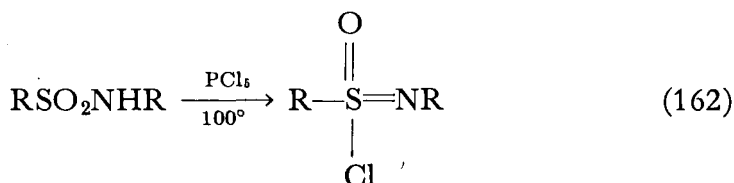
Nitrosation of unsubstituted sulfonamides is analogous to the nitrosation of carboxamides, and gives nitrogen and the free acid (Eq. 160);



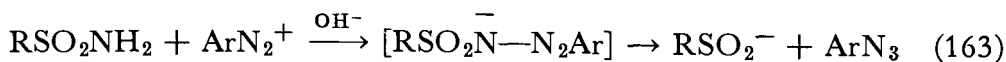
monosubstituted sulfonamides give N-nitroso amides, of use in the preparation of diazo alkanes^{100b} (Eq. 161).



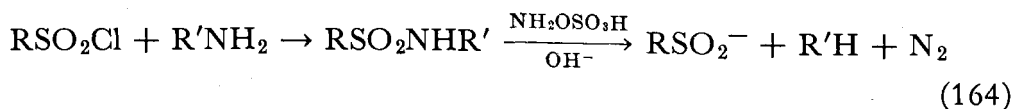
Phosphorus pentachloride converts monosubstituted sulfonamides to sulfonimidoyl chlorides, analogous to carbonimidoyl chlorides^{100c} (Eq. 162); these products are distillable oils that react only sluggishly with water.



The halogenation of sulfonamides to N-haloamides by means of ionic halogenating agents such as hypochlorous acid is general. The reaction has some commercial use in the preparation of halogen carriers for use as bleaching agents and disinfecting agents, such as N-chloro-*p*-toluenesulfonamide, "Chloramine-T." Another example of electrophilic attack on sulfonamide nitrogen is the condensation with diazonium salts. The sulfonyltriazenes initially formed break up in the reaction medium by eliminating sulfinate ion, producing an aryl azide¹⁰¹ (Eq. 163). A

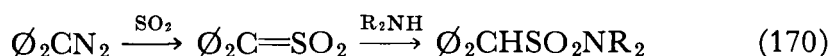


reaction that formally, if perhaps not mechanistically, belongs in this class is the attack of hydroxylamine-O-sulfonic acid on monosubstituted sulfonamides.¹⁰² The N-substituent appears as hydrocarbon, and the net result of the reaction when combined with sulfonylation of a primary amine is replacement of an amino group by hydrogen (Eq. 164). Pre-

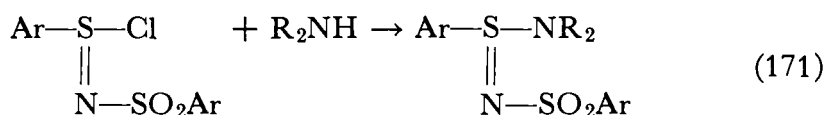


sumably a sulfonyl hydrazide, $\text{RSO}_2\text{NR}'\text{NH}_2$, is an intermediate, and cleaves to sulfinate and a transient alkyl diimide.

PREPARATION ^{94, 99} Sulfonamides are almost invariably prepared by acylation of amines with sulfonyl chlorides, or alkylation of salts of unsubstituted sulfonamides. It should be noted that esters of sulfonic acids are alkylating agents and not acylating agents, and are of no value in preparing sulfonamides. In cases where an especially active α -hydrogen is present, such as in diphenylmethanesulfonyl chlorides, the reaction of the sulfonyl chloride with amines may give poor results, apparently owing to C-acylation of some of the sulfonamide first formed. In such situations, the sulfonamides are best made from diazoalkanes, by reaction with sulfur dioxide and amines ¹⁰⁵ (Eq. 170).



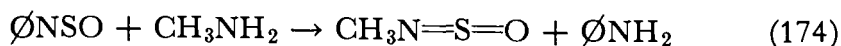
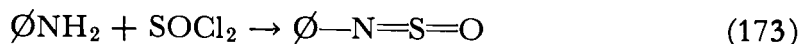
Sulfonimidyl amides ¹⁰⁶ are made by reaction of sulfonimidyl chlorides with amines (Eq. 171).



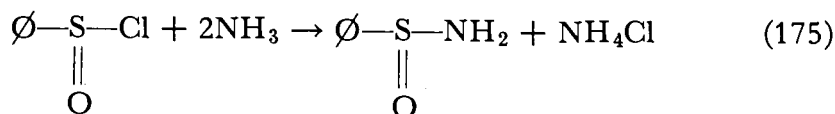
Sulfamides are usually prepared by reaction of sulfamyl chlorides, $\text{R}_2\text{NSO}_2\text{Cl}$, with amines. Sulfamic acids can be prepared in a variety of ways, including sulfonation of amines with sulfur trioxide or sulfuryl chloride. The reaction of hydroxylamines with sulfur dioxide gives sulfamic acids, and can take place during the reduction of nitrobenzenes with sulfites, giving rise to phenylsulfamic acids (Eq. 172).



Thionyl imines are prepared by the reaction of thionyl chloride with amines, or by an exchange reaction between thionylaniline and primary amines (Eqs. 173, 174). Sulfinamides are prepared by the usual acid



chloride-amine reaction ⁹³ (Eq. 175).



HALOAMINE DERIVATIVES

NOMENCLATURE AND INTRODUCTION The haloamines are both formally and chemically amides of the hypohalous acids, and are therefore included in this chapter; the halogens are so-called "positive halogens," in the same oxidation state as the hypohalous acids. These compounds could quite

logically be named as hypohaloamides, with appropriate indication of substituents, but are by custom almost always named as haloamines. Although the International Union of Chemistry and *Chemical Abstracts* rules provide for alphabetical order for substituents, this can lead to confusingly ambiguous names for halo amines, as has been pointed out in Chapter 2. Practicing chemists usually avoid this situation either by prefacing every substituent with the locant "N-", as in "N-chloro-N-methylamine" (CH_3NHCl), or by placing the halogen last in the order of substituents, as in "methylchloramine." Mixed hypohalous-carboxylic and hypohalous-sulfonic amides are usually named as N-halo derivatives of carboxamides or sulfonamides, as in "N-chloro-N-methylacetamide," $\text{CH}_3\text{CONClCH}_3$. N-Halo imines, $\text{R}_2\text{C}=\text{N}-\text{X}$, are discussed along with other imines in Chapter 7.

Haloamines do not appear to occur naturally. They have some practical importance as halogen carriers, and are useful reaction intermediates.

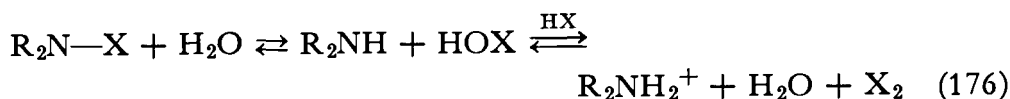
PROPERTIES Like their unsubstituted, inorganic parents, the mono and dialkyl haloamines of chlorine and bromine are volatile, yellow oils, often unstable and even explosive, and possessed of very irritating odors. Dimethylchloramine boils at 46° , and methyldichloramine boils at $59-60^\circ$; perfluoromethylamine, CF_3NF_2 , boils at -78 to -75° , and triphenyl-methyldifluoramine, $\text{C}_6\text{H}_5\text{C}-\text{NF}_2$, melts at $82-83^\circ$. The smaller members are somewhat soluble in water, but far less so than the parent amines; methylchloramine dissolves in eight parts of water. The iodoamines are mostly solids, with reported colors ranging from sulfur yellow for $(\text{CH}_3)_2\text{NI}$ and garnet red for CH_3NI_2 to a blue-black liquid for $\text{C}_2\text{H}_5\text{NI}_2$. The haloamides, RCONHX , usually melt somewhat higher than the corresponding carboxamide, as shown by CH_3CONHCl , mp 112° , and HCONHI , mp 95° . A second halogen lowers the melting point a little, and $\text{CH}_3\text{CONBr}_2$ melts at 100° , compared to CH_3CONHBr , mp 108° .

The effect of halogen substitution on ammonia is parallel to that on water: acid strengthening and base weakening, just as with other acyl groups. The effect of "hypochloryl" chlorine is quantitatively similar to that of an acetyl group, and haloamines are for practical purposes neutral in water solution. Accordingly, N-haloamides should be compared with diacylamides, and they do indeed resemble them in showing acidity similar to phenols if the nitrogen is otherwise unsubstituted, as $\text{RCO}-\text{NH}-\text{X}$.

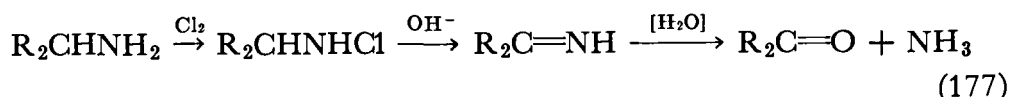
REACTIONS The smaller haloamines are unstable to storage, heat, or light, and may even detonate, especially in the vapor state. This characteristic has hindered their study, and of some, such as methylchloramine, no physical constant is known accurately. N-Chloro- and N,N-dichloro-aniline are unstable oils that spontaneously isomerize to *o*- and *p*-chloroaniline.¹⁰⁷

Hydrolysis of haloamines is quite easy, and they equilibrate slowly

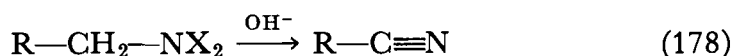
with amine and hypohalous acid; in the presence of acid, the hypohalous acid is further converted to halogen (Eq. 176).



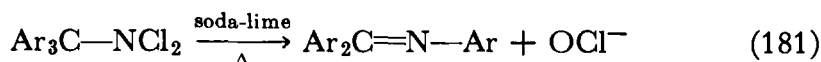
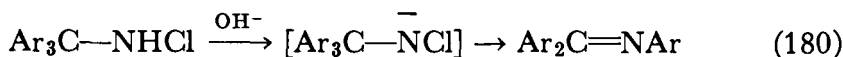
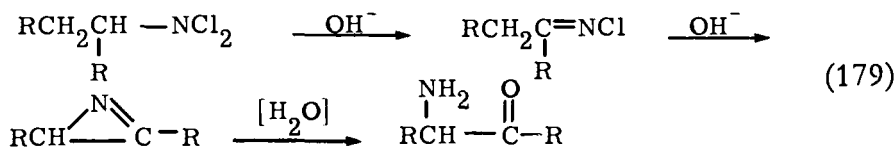
The action of bases is dominated by elimination of HX, which may occur in various ways. If the α -carbon bears a hydrogen, elimination with the formation of a C—N double bond occurs.¹⁰⁸ By this means amines are converted to ketones (Eq. 177). This process can occur



twice with dihalo derivatives of primary alkyl amines, giving rise to nitriles^{109a} (Eq. 178). When, however, there is only one α hydrogen,



the intermediate N-chloro ketimine may be converted to an azirine, which on hydrolysis yields an α -amino ketone^{109b,c} (Eq. 179). If there are no α hydrogens, rearrangement to ketimines occurs^{109d,e} (Eqs. 180, 181).

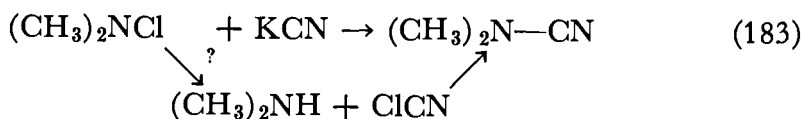


The reaction has received little attention, and all that can be said is that electronic influences on the choice of migrating group are not pronounced.

Triphenylmethyldifluoroamine is cleaved by concentrated sulfuric

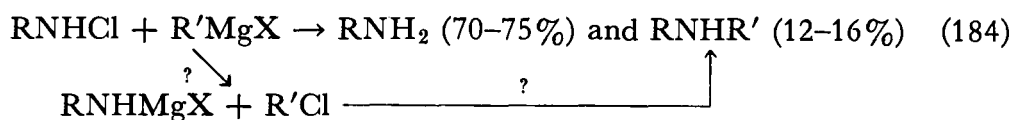


acid into triphenylcarbinol and difluoroamine¹⁰⁹ (Eq. 182). Hydrolytic displacement on nitrogen to produce hydroxylamines has not been reported, but there are some other reactions that may involve nucleophilic displacement on nitrogen. Most of them, however, can equally well be explained by supposing nucleophilic displacement by a carbanion on the positive halogen, followed by a different nucleophilic displacement by nitrogen on carbon (Eq. 183).

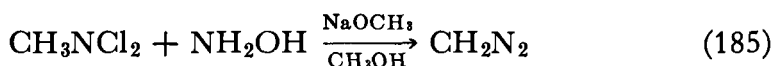


(Possible Paths for the Reaction of Cyanide with Chloroamines)

Grignard reagents¹¹⁰ react effectively as reducing agents, which can reasonably be interpreted as a nucleophilic attack on the halogen atom by the potential carbanion of the Grignard reagent. The small amounts of secondary amines produced in these reactions could result from nucleophilic attack on nitrogen, but can also be explained by interaction between alkyl halide and magnesium amide produced from initial attack on halogen (Eq. 184).

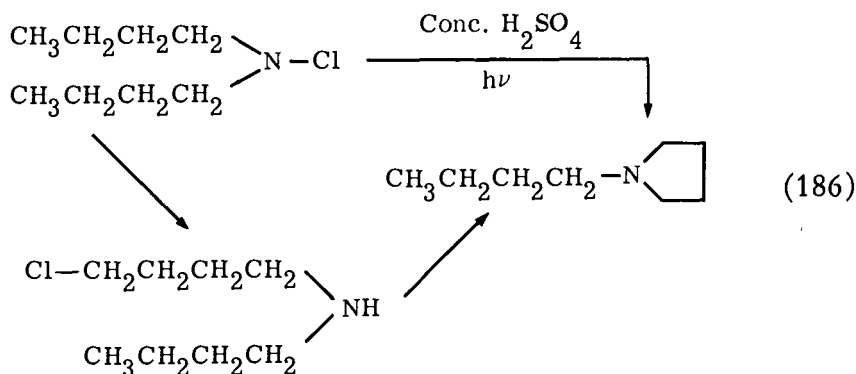


Hydroxylamine in the presence of sodium methoxide converts methyl-dichloramine to diazomethane,¹¹¹ a reaction whose steps have not yet been identified (Eq. 185).



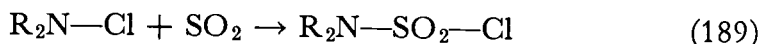
Reducing agents, such as hydriodic acid, in general replace halogen by hydrogen.

The most interesting reactions of haloamines appear to be free-radical in nature. They involve attack at the end of a saturated carbon chain, usually with ring closure. Dibutylchloramine, for example, is converted by concentrated sulfuric acid to N-butylpyrrolidine (Eq. 186). Ultra-

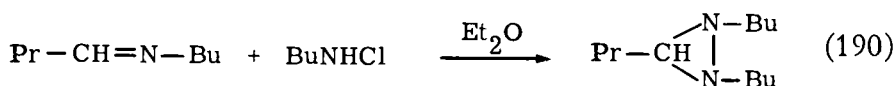


violet radiation aids the reaction, and 4-chlorodibutylamine is an intermediate that can be isolated.¹¹² This synthesis of pyrrolidines, sometimes called the Hofmann-Loeffler or Loeffler-Freytag reaction,¹¹³ gives high enough yields to be of preparative value. It is believed to occur through free-radical cleavage of the N—Cl bond in the protonated haloamine,

The conversion of chloramines to sulfamyl chlorides by reaction with sulfur dioxide ¹¹⁵ (Eq. 189) is also possibly free-radical in nature.



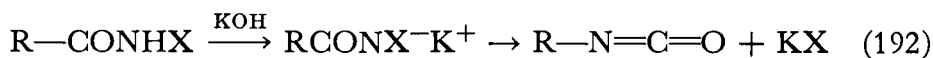
Aldimines and ketimines react with monosubstituted chloramines (as well as with chloramine itself) to produce aziridines, ^{109c} remarkably easily (Eq. 190). In the presence of aqueous alkali, however, aldimines give



rise to amides instead; aldehydes themselves give the same reaction (Eq. 191).



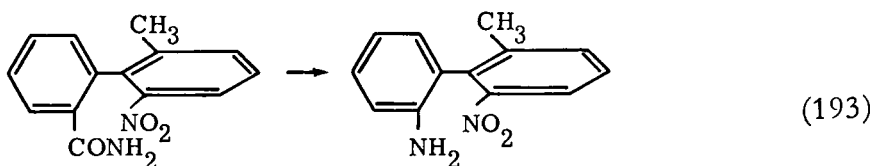
N-Haloamides are also characterized by having so-called positive halogen. In the absence of reducing agents (such as alcohol), the halogen is not precipitated by silver nitrate. N-Halo carboxamides otherwise unsubstituted are acidic enough to dissolve in aqueous alkali as salts. Such salts can be isolated if handled carefully enough, but they rearrange to isocyanates with elimination of alkali halide very easily (Eq. 192),



sometimes even explosively in the solid state. This is the Hofmann rearrangement, the key stage in the Hofmann degradation of amides to amines of one less carbon. ¹¹⁶ Although the rearrangement is often formulated in two steps, with an acyl azene, $R-CON$, as a discrete intermediate, there is as yet no compelling evidence for it, and the migration of R from C to N must follow very fast upon the loss of X^- , if it is not actually simultaneous with it.

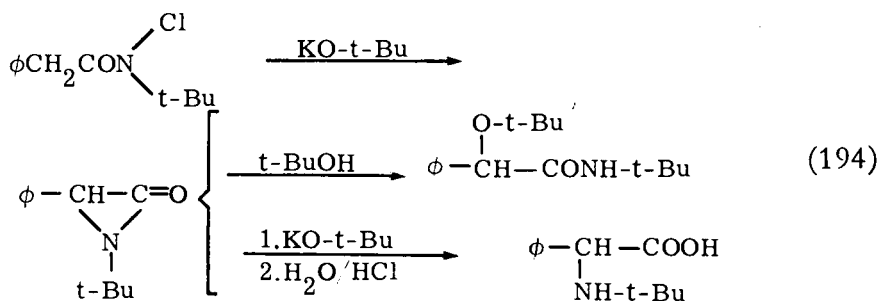
Migration is an internal process, and the migrating group has been shown in numerous experiments never to become a free entity of any sort. If the α -carbon is a site of optical asymmetry, configuration is strictly retained. The most all-encompassing evidence for intramolecularity is in the form of experiments with optically active biphenyls, in which the asymmetry depends on interference with rotation attributable to groups on the *ortho* positions. When one of these groups is a carboxamide, the asymmetry is retained during conversion to an amino group by the Hofmann degradation, showing that rotation continues to be blocked by the

attached groups at all stages in the process (Eq. 193). As the Hofmann

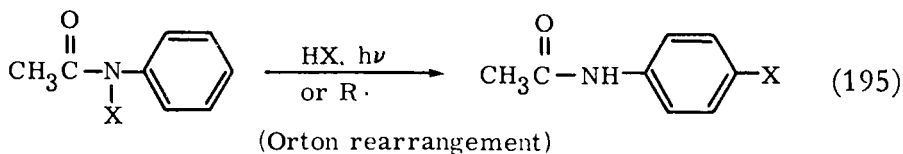


(optical asymmetry retained in Hofmann rearrangement)

degradation is ordinarily carried out for preparative purposes, of course, none of these intermediates is isolated, and the amide is treated with hypohalite in aqueous alkali and converted all the way to amine by subsequent hydrolysis of the isocyanate. N-Alkyl haloamides, which have no acidic hydrogen and cannot form salts, do not undergo the Hofmann rearrangement. Their chemistry is not essentially different from that of the haloamines, although N-chloro-N-*tert*-butylphenylacetamide is an exceptional case, forming an α -amino acid and an α -alkoxy amide through the intermediacy of an α -lactam ¹¹⁷ (Eq. 194).

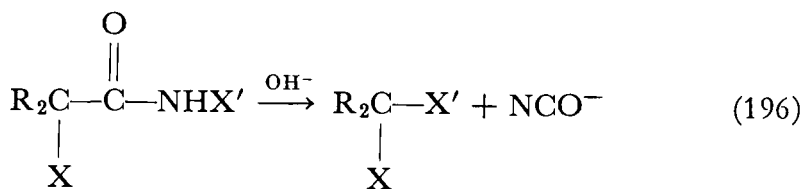


N-Haloanilides, on the other hand, undergo halogen migration from nitrogen to the benzene ring very easily, giving *o*- and *p*-haloanilides ¹¹⁸ (Eq. 195). This reaction is sometimes called the Orton rearrangement.



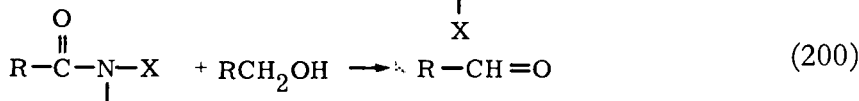
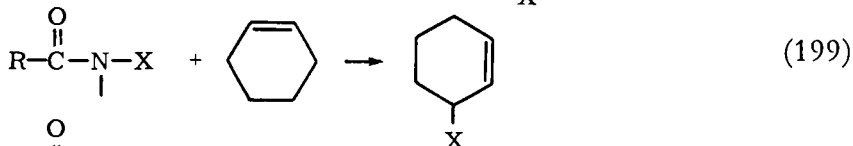
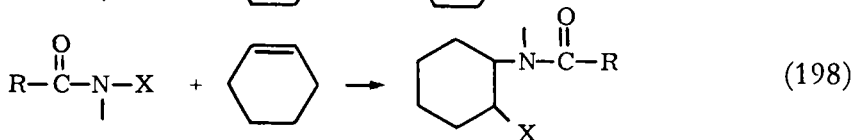
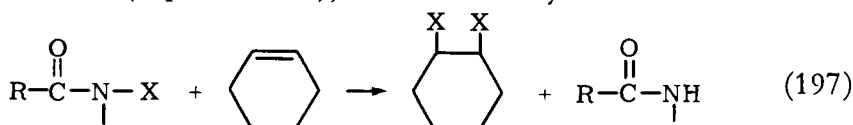
The question whether the process is intermolecular or intramolecular has been a controversial subject ever since the discovery of the reaction, and even now, all that can be said is that an ionic, intermolecular reaction catalyzed specifically by HX is one demonstrated possibility, and a free-radical path, initiated by light or such substances as benzoyl peroxide, is another.

Some α -halo N-haloamides undergo a different type of rearrangement, in which an N-to-C migration of halogen also occurs ¹¹⁹ (Eq. 196).



The reaction is stereospecific with retention of configuration at the α -carbon, and experiments with isotopically labeled bromine have shown the reaction to be intramolecular.

N-Halo imides (diacylamides), as exemplified by N-bromosuccinimide, and some N-haloamides, show special halogenating reactions that have made them important reagents for synthesis in recent years.¹²⁰ They may react by either ionic (heterolytic) or free-radical (homolytic) cleavage of the N—X bond (Eqs. 197–200), but in virtually all cases the result is

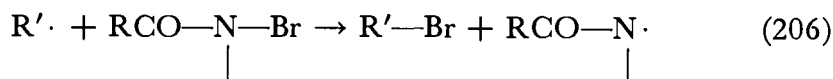
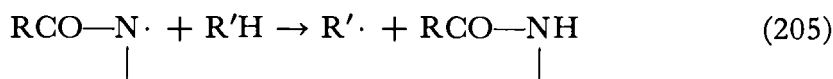
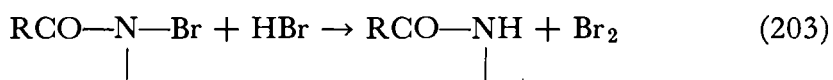
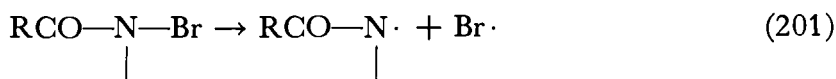


the regeneration of the parent nonhalogenated imide (or amide) and the halogenation of some other substance. An exceptional reaction is addition to a carbon-carbon double bond, halogen becoming attached on one side, amido on the other, forming β -haloalkyl amides; such products have only rarely been isolated¹²¹ (Eq. 198).

Allylic halogenation, sometimes called the Wohl-Ziegler reaction, is the outstandingly valuable reaction among the possibilities. Its occurrence is sensitive to both the structure of the N-halo compound and to the reaction conditions, and although a great many variations have been tried, N-bromosuccinimide suspended in carbon tetrachloride has so far remained the reagent of choice. Neither N-chloro nor N-iodo reagents show the reaction to a useful degree. Solvents that dissolve N-bromosuccinimide appreciably favor the competing reactions; free-radical initiators, such as azoisobutyronitrile (see Chapter 12) or benzoyl peroxide, promote allylic halogenation, whereas free-radical scavengers, such as quinone or oxygen, hinder it. In contrast to N-bromosuccinimide, most

bromoamides and imides react predominantly by adding bromine to double bonds.

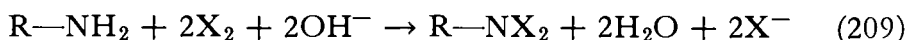
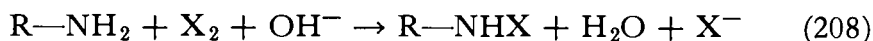
There is general agreement that allylic halogenation is a free-radical process, depending for its success on homolytic cleavage of the nitrogen-halogen bond. According to one view,^{120a} reaction on the surface of solid haloamide is required, with the result that the occurrence of allylic halogenation is governed by the solubility and the molecular geometry of the haloamide, as well as by the polarity of the nitrogen-halogen bond. Alternatively, it has been proposed¹²² that allylic halogenation is the result of specific kinetic conditions, the function of the haloamide being to provide and maintain a very low concentration of free halogen in a nonpolar medium, while also preventing the build-up of an appreciable concentration of hydrogen halide. The reactions that may be involved are as follows (Eqs. 201–207):



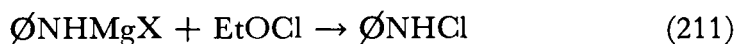
Steps (2) through (4) constitute one possible chain-reaction circuit, and steps (5) and (6) constitute another. When the reversal of step (2) is retarded by keeping the concentration of HBr low, the kinetics support the first alternative; bromine, N-bromosuccinimide, and its tetramethyl and tetrafluoro derivatives all show the same Hammett reaction constant, ρ , toward substituted toluenes.^{122c}

N-Halosulfonamides are also well-known substances,⁹⁴ whose behavior is rather similar to the N-halocarboxamides. N-Chloro-*p*-toluenesulfonamide, known as chloramine-T, has use as a water-purifying agent, in which capacity it simply acts as a source of positive ("active") chlorine. Although the common reaction of N-halosulfonamides is oxidation or ionic halogenation, addition to olefins to form β -haloalkyl sulfonamides has also been observed.

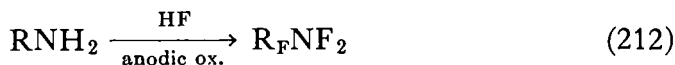
PREPARATION The preparation of N-halo compounds is nearly always accomplished by the reaction of the free halogen or metal or alkyl hypohalite on the parent nitrogen compound, commonly in aqueous solution ^{110, 123} (Eqs. 208–210). Excess halogen will usually place a second



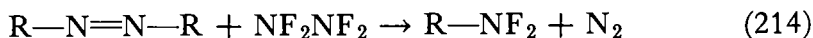
halogen atom on nitrogen. The reactions are usually carried out in the presence of sufficient base to neutralize the mole of hydrogen halide also produced, but halogenation of amides has been accomplished with pronounced success even in such a strongly acidic medium as trifluoroacetic acid.¹²¹ N-Halogenation is reversible by hydrolysis, however, and appropriate care must be taken in handling and purifying N-halo compounds in order to maintain their halogen content. The preparation of N-chloroaniline has been reported by the action of magnesium anilide with ethyl hypochlorite ¹⁰⁷ (Eq. 211).



Fluoroamines are best prepared ¹²⁴ by anodic fluorination of amines or nitriles in liquid hydrogen fluoride; the organic substituents are also fully fluorinated by this procedure (Eq. 212). Alternatively, cobalt



trifluoride can be used. Reaction of alkyl iodides or azo compounds with perfluorohydrazine ($\text{F}_2\text{N—NF}_2 \rightleftharpoons 2\text{F}_2\text{N}\cdot$) gives N,N-difluoroamines in which the organic substituents are unfluorinated ¹²⁵ (Eqs. 213, 214).



AMIDES OF ACIDS DERIVED FROM OTHER ELEMENTS

Amides are known in which nitrogen is attached to most other elements that give rise to oxy acids. The most important are the amides of the acids derived from phosphorus.¹²⁶ Their chemistry is of less general concern to the organic chemist than that of the amides so far discussed, although there is an enormous amount of literature on amides of phosphorus acids, owing to their widespread and growing industrial importance. Not only full amides, such as hexamethylphosphoric triamide,

OP(NMe₂)₃, and hexamethylphosphorous triamide, P(NMe₂)₃, are known, but also the various corresponding amidic acids. The amides and amidic acids derived from phosphonic acids, R—PO(OH)₂, and phosphonous acids, R—P(OH)₂, are also known in large variety. Works on phosphorus chemistry should be consulted for further information.¹²⁷

Very little is known about the amides of silicon acids. The only known examples¹²⁸ are derivatives of the ortho acid structure, such as (t-BuO)₂Si(NH₂)₂ and ArSi(NH₂)₃.

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chapter
five

Nitriles and Isocyanides

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NITRILES

A. Nomenclature and General Remarks

Compounds of the type $R-CN$ are known as nitriles or as alkyl (aryl) cyanides. The naming of individual compounds as cyanides follows the familiar patterns, but it is not preferred for systematic nomenclature because it disguises the true length of the carbon chain. According to the I.U.C. agreement, nitriles should be named on the basis of the name of the corresponding acid that could be formed by hydrolysis, the terminal “-ic” being replaced by “-nitrile” or “-onitrile.” Thus CH_3CN (“methyl cyanide”) is “acetonitrile,” and $CH_3(CH_2)_4CN$ (“*n*-amyl cyanide”) is “hexanonitrile.” This system is equally applicable to the pre-Geneva names for the acids of course, and hexanonitrile, for example, is sometimes called “capronitrile.” It should be clearly understood that the ending “-nitrile” implies no additional carbons beyond those already indicated in the stem name. For this reason, “-carbonitrile” must be used when it is necessary to indicate the presence of an additional carbon,

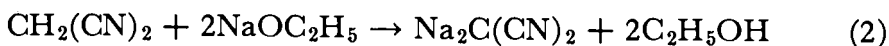
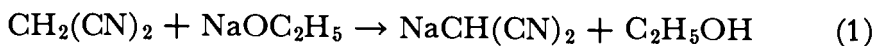
and cyclohexyl cyanide, for example, must be called "cyclohexane-carbonitrile." It is sometimes desirable to denote the —CN group by a prefix, in which case "cyano-" is used, as in "*p*-cyanobenzoic acid."

Nitriles occur naturally; the best known example is probably amygdalin, a glycoside of α -hydroxyphenylacetonitrile, found in bitter almonds. Nitriles have great commercial importance, primarily as intermediates for the preparation of other compounds. The toxicity of most nitriles is not exceptional, and not to be judged by the example of hydrogen cyanide.

B. Properties

Nitriles have considerably lower boiling and melting points than the corresponding acids, as might be expected in consideration of the absence of hydrogen-bonding possibilities, but the boiling points are still relatively high, being not far from those of the alcohols of the same number of carbons. Acetonitrile, bp 82° , mp -46° ; and benzonitrile, bp 191° , mp -13° , are representative. Hexacyanoethane, $(\text{NC})_3\text{C—C}(\text{CN})_3$, is a solid that decomposes above 150° with elimination of cyanogen.¹ Acetonitrile is miscible with water, but nitriles with more than five carbons are practically insoluble. The aliphatic nitriles have large dipole moments (about 3.9 D for CH_3CN), and the dielectric constant of acetonitrile, 37.5 at 20° , is about half that of water. Acetonitrile is thus a highly polar solvent, and is capable of dissolving many ionic substances as well as most ordinary organic compounds.

Nitriles are for ordinary purposes completely neutral substances. The basicity of the nitrogen atom is so low that nitriles do not form well-defined salts even in the absence of water, although they evidently undergo some protonation by strong acids, and form addition compounds with dry hydrogen chloride. The α -hydrogens of aliphatic nitriles react with very strong bases, such as sodium amide, forming salts. Acetonitrile has an estimated² acidity constant, K_a , of 10^{-18} , and it can be said that mononitriles are similar to alcohols in acid strength, whereas malononitriles, with two cyano groups on the same carbon, form sodium salts readily with sodium alkoxides (Eqs. 1, 2). Tricyanomethane (cyanoform),³ $\text{HC}(\text{CN})_3$,



is a fairly strong acid; it probably exists largely as the ketenimine tautomer, $(\text{NC})_2\text{C}=\text{C}=\text{NH}$.

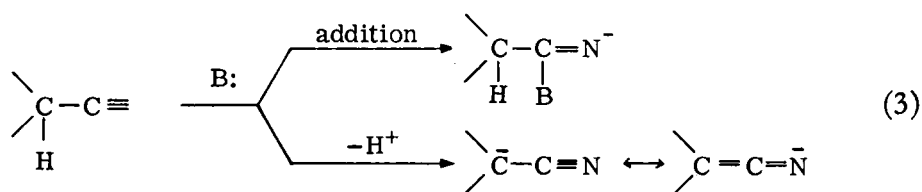
The triple bond of nitriles has a stretching frequency in the infrared at *ca.* 2250 cm.^{-1} , the region where other triple bonds absorb. The nitrile structure would be represented in molecular orbital terms with two π bonds and *sp* hybridization at both the carbon and the nitrogen.

C. Reactions

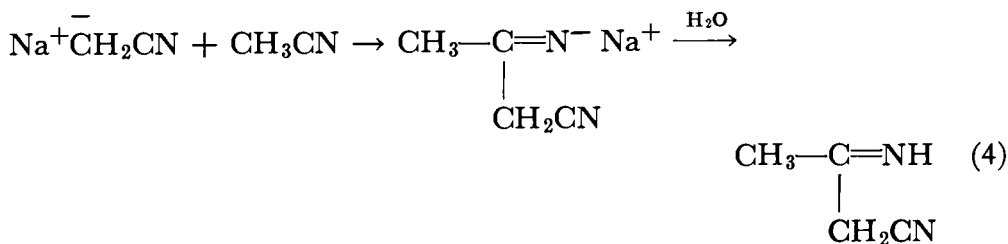
Although nitriles are not basic enough to form salts with aqueous acids, they do form addition compounds with strong acids when water is absent. The nature of such compounds has been a controversial matter, for they may be formulated either as imidic acid derivatives or as true salts, and they usually form in the proportion of two molecules of acid to one of nitrile. The last word has undoubtedly not been written on the subject, but it appears ⁴ on the basis of their electrical conductivity and spectral properties that they are either salts of imidoyl derivatives, such

as $\text{R}-\text{CBr}=\text{NH}_2^+ \text{Br}^-$, or acid nitrile salts, such as $\text{R}-\text{C}\equiv\text{NH}^+ \text{HCl}_2^-$.

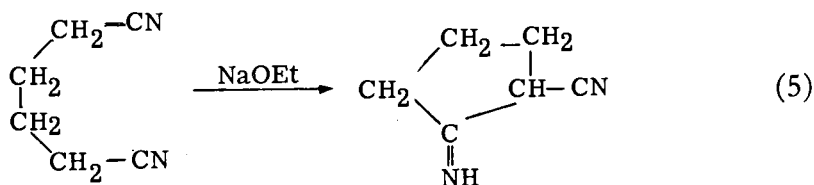
The cyano group is strongly polarized in such a way that the carbon atom is a positive, thus electrophilic, site, and the nitrogen is negative. Nitriles are thus susceptible to attack by bases in two ways: attack at the carbon, resulting in addition, and attack at an α -hydrogen, resulting in proton removal (Eq. 3); proton removal is generally faster.



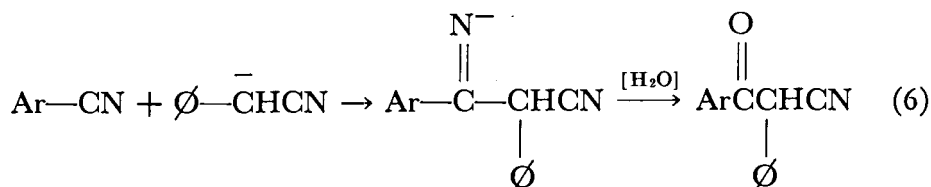
The metal salts of nitriles are highly reactive and in general not stable to storage. In particular, the anion will act as a base toward the cyano group of another molecule, and will slowly add, in a manner analogous to the Claisen condensation of esters. The products after neutralization are the imines of β -keto nitriles (Eq. 4); that from acetonitrile is often



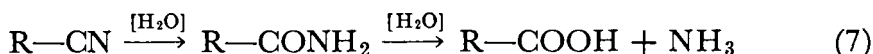
called "diacetonitrile." An important application of this, the Thorpe reaction (Eq. 5), due to Ziegler, is the synthesis of very large rings from



α , ω -dinitriles by treatment with one mole of a strong base.⁵ High dilution is necessary when rings larger than six atoms are to be made, in order to make cyclization predominate over intermolecular reaction, which would lead to polymer. Condensation between two different nitriles can be accomplished by adding the sodium salt of one to the other (Eq. 6).



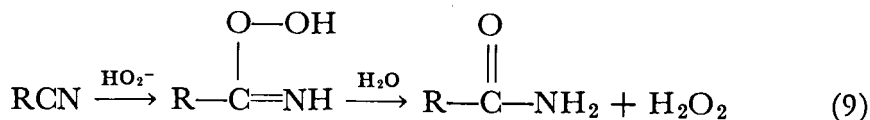
Nitriles are hydrolyzed by water in the presence of acid or base in two stages: first to amides, and then to carboxylic acids (Eq. 7). The relative



rates of the two stages depend on both the structure of the nitrile and the experimental conditions; obviously, when the second stage is faster than the first, the intermediate amide cannot be isolated, a situation that commonly obtains with aliphatic nitriles. Nevertheless, aliphatic nitriles have been successfully hydrolyzed to amides by use of basic anion-exchange resins. Dissolving aromatic nitriles in concentrated sulfuric acid and then precipitating with ice is a fairly general way to convert them to amides (Eq. 8).

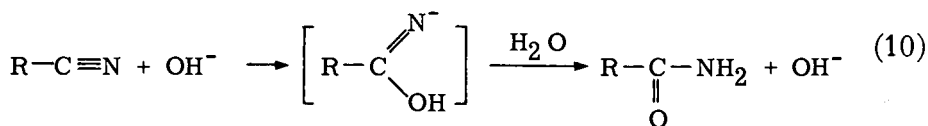


Nitriles vary greatly in their ease of hydrolysis, and many aromatic ones, particularly those that are hindered by *ortho* substituents, are extremely difficult to hydrolyze. Concentrated mineral acids, such as sulfuric or orthophosphoric, are often successful. Many nitriles that are hydrolyzed only sluggishly by aqueous alkali can be hydrolyzed readily when hydrogen peroxide is also added⁶ (Eq. 9); the effective reagent, HO_2^- , is a much stronger nucleophile.

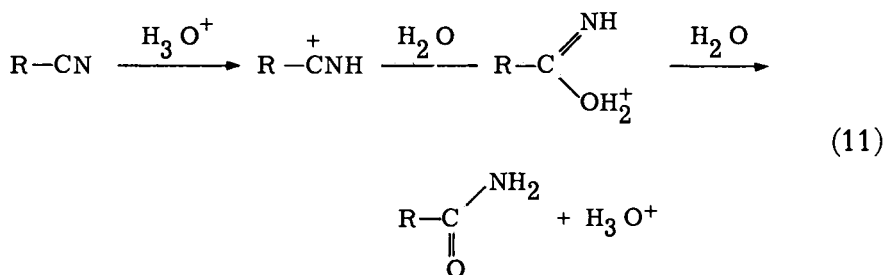


The hydrolysis of nitriles is a case of the addition of a nucleophile to the nitrile carbon. In base-catalyzed hydrolysis, the intermediate addition compound must of course undergo a proton shift and acquire a proton

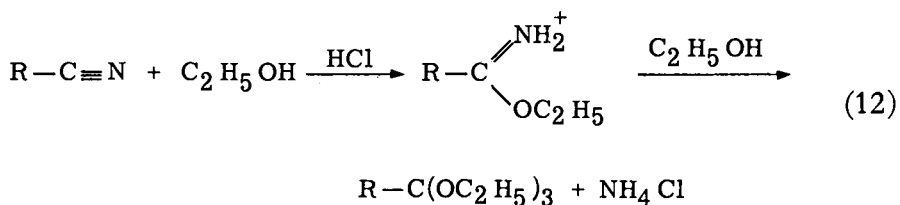
from the environment (Eq. 10). In acid catalysis, it must be the pro-



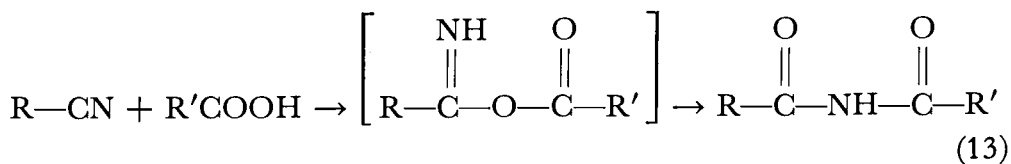
tonated nitrile, $\text{R}-\text{CNH}^+$, that is attacked by a nucleophile, presumably molecular water (Eq. 11).



Nitriles can, of course, add many other types of nucleophiles, such as alkoxides, amines, and carbanions. The addition of alcohols, either as alkoxide, or as neutral alcohol to a protonated nitrile, has already been mentioned in Chapter 4 in connection with the preparation of imidate esters. Alcoholysis of nitriles proceeds in two stages, just as hydrolysis, but since an alkyl group cannot shift nearly so easily as a proton, the nature of the alcoholysis products is different. The reaction is a useful synthesis of imidate esters when only one mole of alcohol is used, and a useful synthesis of ortho esters when excess is used ⁷ (Eq. 12). The reaction

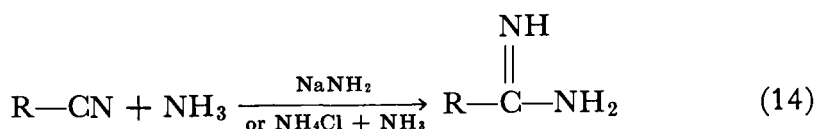


of carboxylic acids when heated with nitriles, to give diacylamides,⁸ and of acid anhydrides to give triacylamides, are examples of solvolyses in which the initial product undergoes rearrangement, the acyl group migrating from O to N (Eq. 13).

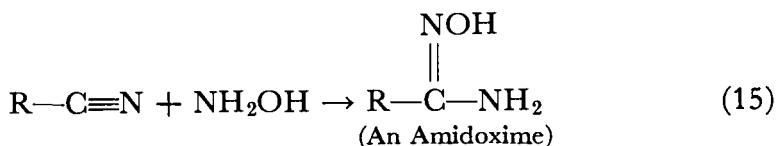


Ammonia and amines add rather difficultly to nitriles, producing amidines. In analogy to hydrolysis, either base (NaNH_2) or acid

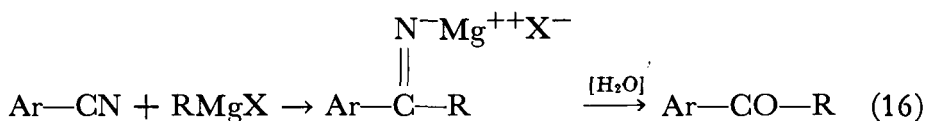
(NH_4Cl) catalysis can be used ⁹ (Eq. 14). Hydroxylamine and hydra-



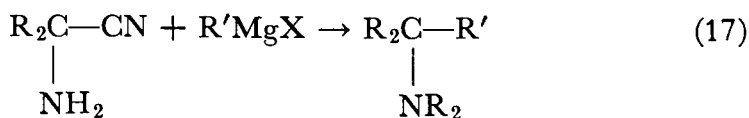
zine, which are stronger nucleophiles than ammonia or amines, add more readily, producing analogues of amidines (Eq. 15).



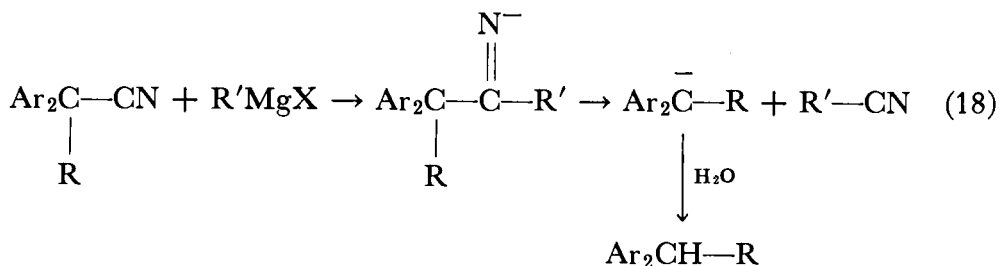
The addition of carbanions to the nitrile triple bond is of great importance. The most familiar case is the addition of Grignard reagents to nitriles to give the magnesium salts of ketimines, which are easily hydrolyzed to ketones (Eq. 16). Electron-withdrawing substituents on the

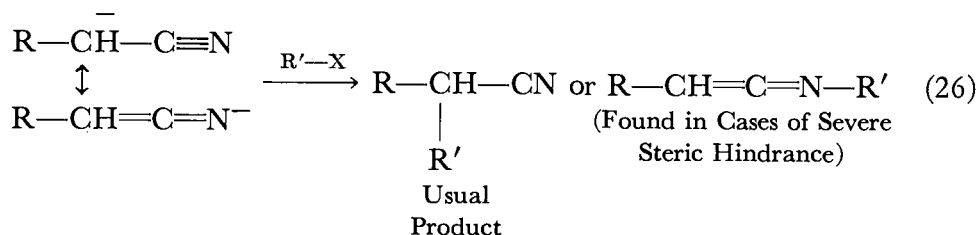


nitrile accelerate the reaction, a fact that is consistent with addition of the carbanion moiety to the nitrile carbon being the slow step.¹⁰ Aryl lithium reagents react far faster than aryl Grignard reagents, whereas alkyl Grignard reagents react distinctly slower. In fact, under ordinary conditions, only half of the alkyl groups react at all, which suggests that the species that first reacts is R_2Mg rather than RMgX . Although this is a fairly general reaction, there are difficulties with nitriles having an α -hydrogen, occasioned by the competing acid-base reaction, and it cannot be considered a reliable way to synthesize ketones from aliphatic nitriles. Acetonitrile, for example, is converted to various condensation products, such as diacetonitrile (β -aminocrotonitrile) and substituted pyridines by treatment with Grignard reagents, and phenylacetonitrile behaves similarly.¹¹ A different sort of reaction, encountered with α -amino nitriles, is sometimes called the Bruylants reaction. The cyano group is completely removed and replaced by the organic moiety of the Grignard reagent ^{12a,b} (Eq. 17). Most α,α -diaryl nitriles also lose their



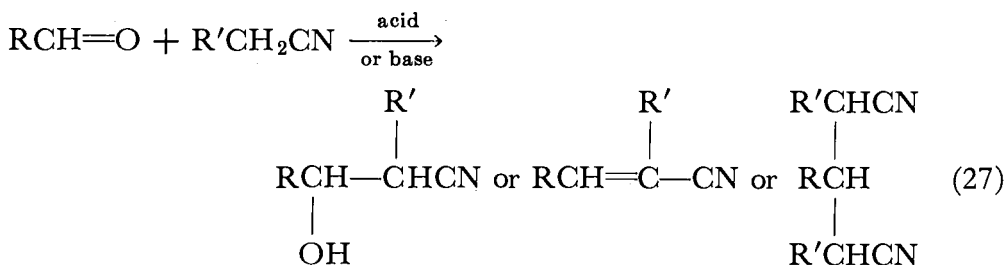
cyano group on reaction with Grignard reagents, but in these cases the cyano group is replaced (after hydrolysis) by hydrogen.^{12c} The reaction can be understood as the separation of an especially stable carbanion from the ketimine anion initially formed (as its magnesium salt) (Eq. 18).



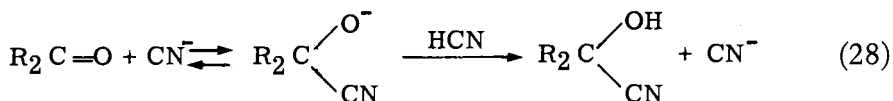


thus produced are not usually isolated, for they rapidly add solvent to form amides or related substances.

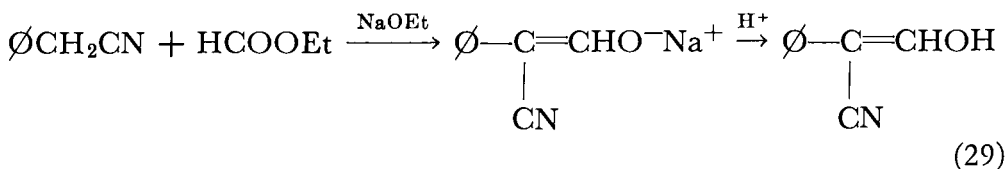
Aldehydes and ketones react with aliphatic nitriles much as they do with other substances possessing active hydrogens and under similar conditions (acid or base catalysis).¹¹ Three types of products may be expected: β -hydroxy nitriles, resulting from simple addition; α,β -unsaturated nitriles, resulting from addition and dehydration, and 1,3-dicyano compounds (glutaronitriles), resulting from addition of a second molecule of nitrile (Eq. 27). Hydrogen cyanide is, of course, a special case.



Although it has no α -hydrogens, it is weakly acidic and adds readily to most aldehydes and ketones to form cyanohydrins (α -hydroxy nitriles). The reaction is catalyzed by traces of base (that is, cyanide ion) (Eq. 28).

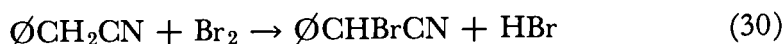


Acyating agents, such as esters or acid chlorides, condense with nitriles at the α -position, if there is base present, producing β -keto nitriles (Eq. 29). This reaction is not essentially different from the Claisen ester

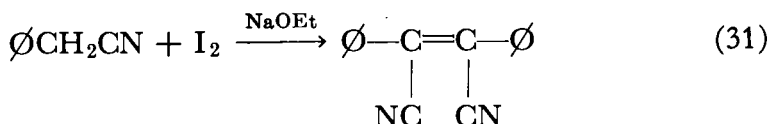


condensation. Base-catalyzed nitrosation and nitration¹⁷ can be carried out in the same way, using alkyl nitrites or nitrates. Ionic halogenation also takes place on the α -carbon, just as it does with other active hydrogen

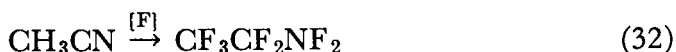
compounds (Eq. 30), such as esters and ketones. Iodine is sometimes



an exception, however, and may cause oxidative coupling (probably as a result of a displacement reaction between initially formed α -iodo nitrile and cyano anion, followed by oxidation) (Eq. 31). Fluorination,¹⁸ best



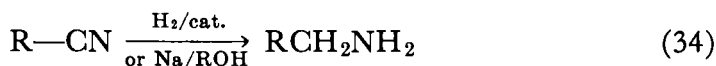
carried out electrolytically in liquid hydrogen fluoride, results in addition to the triple bond as well as replacement of all hydrogens, forming perfluoroalkyl difluoroamines (Eq. 32).



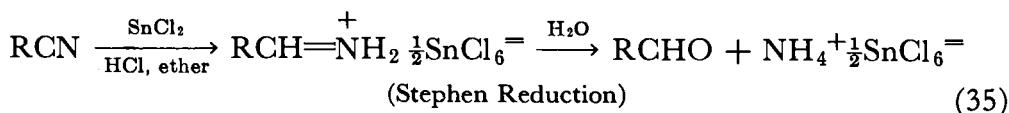
The behavior of hydrogen cyanide toward acylating agents is, of course, exceptional. In the form of its salts or in the presence of pyridine, it reacts to form acyl cyanides (α -keto nitriles),¹⁹ usually rather slowly (Eq. 33).



Reduction of nitriles occurs in two stages, producing either aldimines or primary amines. Complete reduction is the common reaction with catalytic hydrogenation, sodium and alcohol,²⁰ lithium aluminum hydride,²¹ or zinc and alcoholic hydrogen chloride, and constitutes an important preparative method for primary amines (see Chapter 2) (Eq. 34). With stannous chloride in anhydrous, ethereal hydrogen chloride,

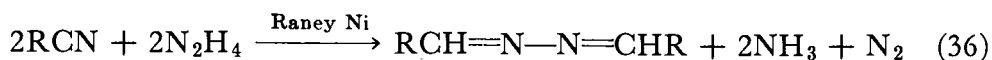


reduction can be stopped in good yield at the aldimine stage (Stephen reduction).²² The aldimines are usually isolated as the chlorostannate salts that form in the reaction mixture. Hydrolysis of these products to aldehydes is usually accomplished without effort, and the over-all process is a valuable aldehyde synthesis (Eq. 35). A different method of reducing



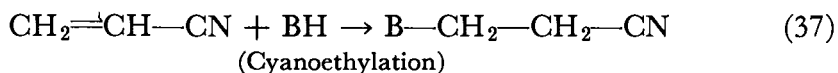
nitriles to the aldehyde stage, of more recent origin, consists of treatment with excess hydrazine and Raney nickel²³; the azine derivative of the aldehyde is the actual product, and is generally obtained in high yields

(Eq. 36). Reduction of nitriles to aldehydes (through the imines) can



also be accomplished with lithium triethoxyaluminum hydride ²⁴ or with hydrogen, formic acid, or sodium hypophosphite and Raney nickel.²⁵

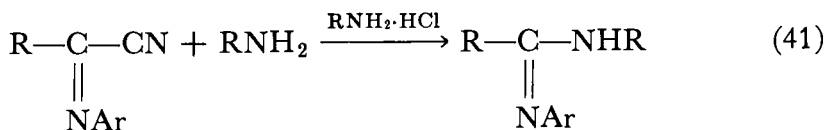
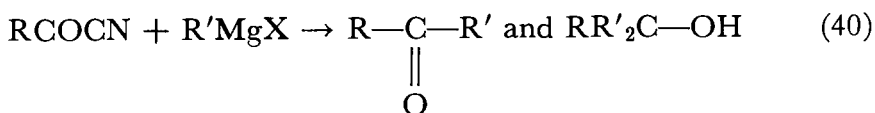
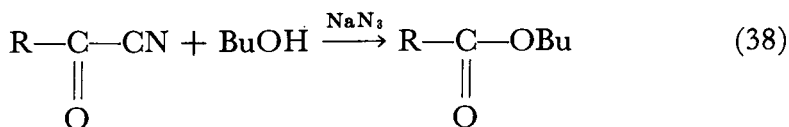
α,β -Unsaturated nitriles have an elaborate chemistry all of their own, resulting from activation of the olefinic double bond by the cyano group. The chemistry of acrylonitrile,²⁶ $\text{CH}_2=\text{CH}-\text{CN}$, a very important intermediate prepared commercially on a large scale, has been especially widely developed. Its most important reaction is "cyanoethylation," by which Michael addition of another substance to the double bond produces β -cyanoethyl derivatives (Eq. 37). Amines, alcohols, and compounds



with reactive methylene groups can take part in such reactions. As a consequence of the polarization of the double bond by the cyano group, the nucleophilic moiety always becomes attached to the β -carbon. Tetracyanoethylene,²⁷ which has an extraordinarily electron-poor double bond, shows many reactions that one is tempted to call unique. It forms intensely colored complexes with most aromatic compounds, is an avid dienophile in the Diels-Alder reaction, and is readily reduced to an anion-

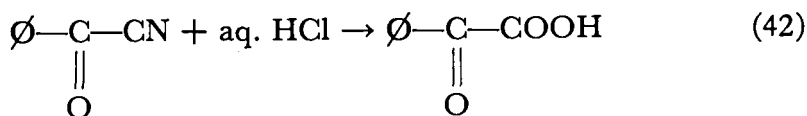
radical, $(\text{NC})_2\dot{\text{C}}-\text{C}^-(\text{CN})_2$.

α -Keto ²⁸ and α -imino ²⁹ nitriles (acyl cyanides) are also atypical of nitriles in general. They readily lose cyanide ion when attacked by nucleophiles, and are thus acylating agents (Eqs. 38-41). This behavior

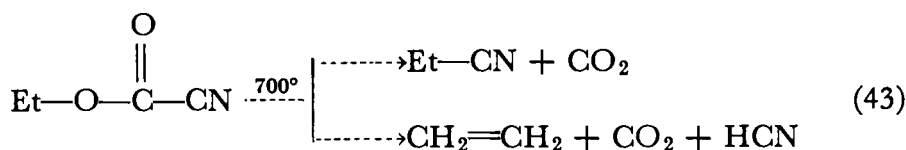


has a distinct preparative value in some instances. In acid solution, however, they behave normally, and can be hydrolyzed to α -keto amides

or acids ³⁰ (Eq. 42). Carboalkoxy cyanides ³¹ (cyanoformate esters) show

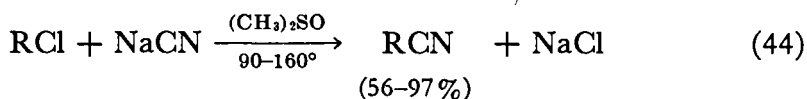


further distinctive behavior on pyrolysis. Two principal reactions compete: simple nitriles are produced by loss of carbon dioxide, and elimination of cyanoformic acid (or its fragments) converts the alkyl group to olefin (Eq. 43).

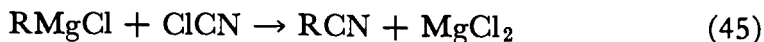


D. Preparation ³²

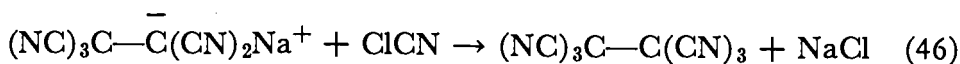
The oldest and simplest preparation of nitriles is alkylation of sodium or potassium cyanide. It is a somewhat sluggish reaction that until recently was largely confined to primary alkyl groups. With dimethyl sulfoxide as solvent, however, both primary and secondary alkyl chlorides can be converted to nitriles in good yields ³³ (Eq. 44). Tertiary alkyl



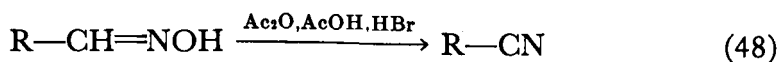
halides, of course, are too resistant to displacement reactions to take part, and usually undergo elimination instead. Silver cyanide cannot be substituted for sodium or potassium cyanide, for it gives isonitriles instead. Acid chlorides, however, give α -keto nitriles by reaction with potassium, silver, or copper cyanides.¹⁹ The converse of these reactions, the treatment of organometallic reagents with cyanogen chloride (but not the bromide or iodide) or cyanogen, can be made to give useful yields of nitriles ³⁴ (Eq. 45). This reaction can be extended to sodium salts of



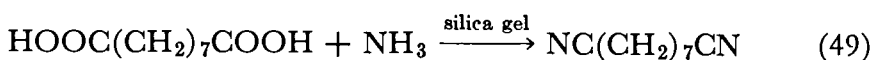
acidic nitriles, as in the synthesis of hexacyanoethane ^{1, 34d} (Eq. 46).



Nitriles may be prepared by dehydrating either amides or aldoximes ³⁵ (Eqs. 47, 48); these reactions are discussed in Chapters 4 and 8. The



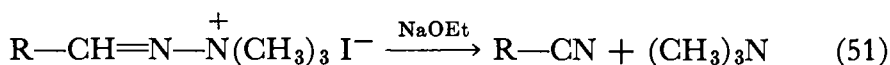
dehydration of amides can also be combined with their formation from acids or esters in a simple catalytic process at somewhat elevated temperatures (Eq. 49); this method is particularly suited to the preparation of



dinitriles. A process related to dehydration of oximes is the Schmidt reaction on aldehydes, which are converted to nitriles by hydrogen azide in the presence of strong acid ³⁶ (Eq. 50). Both the Beckmann rearrange-

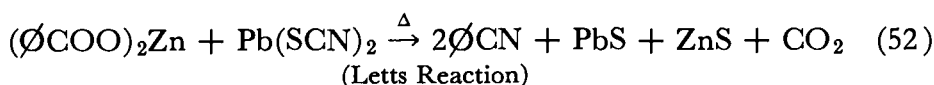


ment of ketoximes and the Schmidt reaction with ketones also give nitriles by fragmentation in special cases, but such methods are only exceptionally of preparative importance. Another elimination reaction leading to nitriles is that of quaternary hydrazones of aldehydes ³⁷ (Eq. 51); the

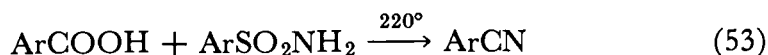


procedure is simple and mild, the yields are good, but the scope and limitations have yet to be explored.

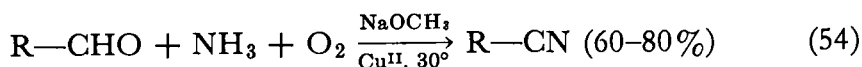
A curious and little used reaction, sometimes known as the Letts reaction, produces nitriles very simply from carboxylic acids. Fusion of the zinc salt of the acid with lead thiocyanate is all that is necessary ³⁸ (Eq. 52). Acids may sometimes be converted to nitriles by an exchange



reaction with acetonitrile, brought about at high temperature in the presence of acidic catalysts.³⁹ The same conversion can be brought about by heating acids with sulfonamides, with or without the aid of phosphorus pentachloride ⁴⁰ (Eq. 53); this reaction appears to be limited



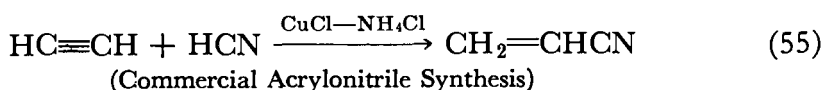
to aromatic compounds. Apparently related is the thermal disproportionation of amides, which is useful in special cases, such as the preparation of sebaconitrile.^{40b} Good yields of nitriles have been obtained by passing oxygen and ammonia into an alcoholic solution of an aldehyde containing a copper compound as a catalyst ⁴¹ (Eq. 54).



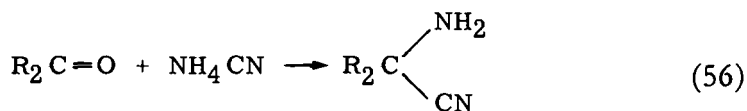
Aliphatic primary amines having an α -methylene group can be converted to nitriles by oxidation, such as by hypohalites,⁴² or by catalytic

dehydrogenation accomplished by passing the hot vapors over nickel, copper, or similar catalysts.⁴³ It is not even necessary to start with an amine, for mixtures of ammonia with an aldehyde or a primary alcohol treated similarly also give nitriles. These reactions are of little importance in the laboratory, although they have obvious industrial capability.

The addition of hydrogen cyanide to multiple bonds can be a valuable nitrile synthesis. Ordinary olefins are too inert to be useful, but acetylene reacts readily with hydrogen cyanide in the presence of cuprous chloride-ammonium chloride solution as catalyst, producing acrylonitrile in high yield (Eq. 55). Millions of pounds of acrylonitrile are produced yearly



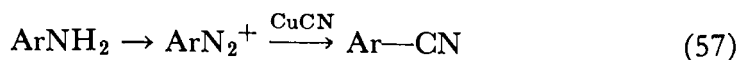
by this reaction. The addition of hydrogen cyanide to carbon-oxygen double bonds to produce α -hydroxy nitriles⁴⁴ (cyanohydrins) has already been mentioned. These substances can be dehydrated to α,β -unsaturated nitriles. When the addition to a carbonyl group is carried out in the presence of ammonia or amines, α -amino nitriles are produced.⁴⁵ This is known as the Strecker reaction, and is important in the synthesis of α -amino acids (Eq. 56). The use of cyanoethylation as a method for



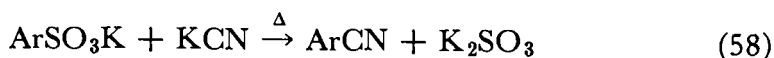
(Strecker reaction)

preparing more elaborate nitriles from acrylonitrile has already been mentioned.²⁶

There are several reactions that are essentially confined to the preparation of aromatic nitriles. The most widely known of these is the Sandmeyer reaction,⁴⁴ in which a diazonium salt reacts with cuprous cyanide (see Chapter 11) (Eq. 57). An old but much less widely applicable reaction is fusion of a benzenesulfonate salt with potassium cyanide

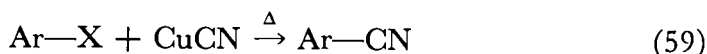


or ferricyanide⁴⁷; this is apparently a forced electrophilic substitution on the benzene ring (Eq. 58). Aryl halides are generally too inert to undergo

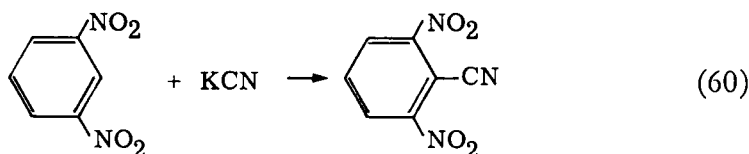


reaction with potassium cyanide, unless there is strong activation by electron-withdrawing groups, as in 2,4-dinitrochlorobenzene. However, even nonactivated halogen atoms can be replaced by cyanide by heating

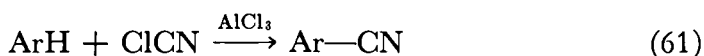
with cuprous cyanide ⁴⁸ (Eq. 59). It is a useful reaction, but must be



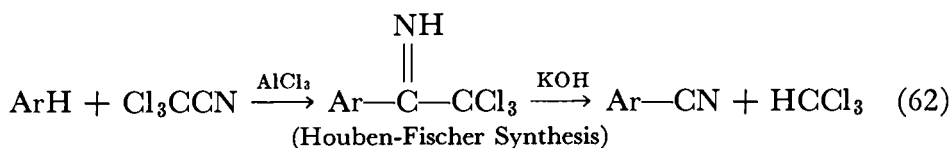
carried out with caution, since it requires strong heating to get started, but thereafter may be autocatalytic. Nucleophilic replacement of hydrogen can also be preparatively useful, as in the conversion of *m*-dinitrobenzene to 2,6-dinitrobenzonitrile ⁴⁹ (Eq. 60).



The Friedel-Crafts type of reaction has been adapted to nitrile synthesis in two ways. Cyanogen chloride will react with aromatic hydrocarbons in the presence of aluminum chloride to give benzonitriles directly (Eq. 61), but the reaction gives poor yields unless the reagents



are freshly prepared.⁵⁰ In the Houben-Fischer synthesis, trichloroacetonitrile is used in an initial step to give a trichloromethyl aryl ketimine. These compounds are cleaved by alkali in the same way as are trichloromethyl ketones in the haloform reaction, giving nitriles and chloroform ⁵¹ (Eq. 62).



ISOCYANIDES

A. Nomenclature

Since isocyanides have a carbon skeleton different to that of nitriles, the longest carbon chain being one less than that in the nitrile isomer, their systematic nomenclature must be different. They are to be regarded as derivatives of amines, which they give on hydrolysis, and not as derivatives of acids. The method used by *Chemical Abstracts* is to name the alkyl or aryl group and follow it with "isocyanide" as a separate word as in "methyl isocyanide," CH_3NC . Two other words, "carbylamine" and "isonitrile" are sometimes used instead of "isocyanide," especially in the older literature, but it would be best to let them peacefully fade away.

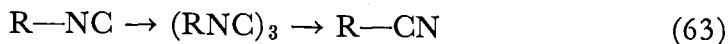
B. Properties

The common isocyanides are liquids, almost insoluble in water, and having boiling points lower by about 25° than the isomeric nitriles (but much higher than hydrocarbons of similar molecular weight); methyl isocyanide boils at 59° and melts at -45°, and phenyl isocyanide boils at 166°. They are not basic in the sense of forming salts, but their fundamentally basic nature is shown by the fact that they react readily with acids (to give addition or hydrolysis products), and form complexes with many heavy-metal cations. In such complexes, which are often remarkably stable, the attachment to metal is through the end carbon atom. It is worthy of notice that the isocyanide carbon also plays the role of acceptor in forming hydrogen bonds, the only situation known where carbon does this.⁵²

The bond structure of isocyanides has been a subject of earnest discussion for a long time. Before the advent of the electron-pair theory of chemical binding, isocyanides were considered to be simply examples of a lower valence state of carbon. The electron-octet concept was

adapted to isocyanides in a formula with charge separation: $\text{R}:\overset{+}{\text{N}}::\overset{-}{\text{C}}:$. This corresponds to a triple bond in which one third (i.e., one electron pair) is coördinate, alternatively represented as $\text{R}-\text{N}\equiv\text{C}$. The infrared spectra of isocyanides show characteristic absorption in the 2120–2140 cm^{-1} region, close to that shown by other triple-bonded compounds, such as nitriles and acetylenes. It should be noted that isocyanides are isoelectronic with carbon monoxide, to which they show many resemblances. The C—N—C system in isocyanides is linear, and the terminal N—C bond distance is almost the same as in nitriles (1.167 Å in CH_3NC).⁵³ Isocyanides are less soluble in water than nitriles, and methyl isocyanide, for example, dissolves to the extent of only 10% at 15°.

The dipole moment of methyl isocyanide, 3.6 D, is large, but nevertheless slightly less than that of acetonitrile. The isocyanide structure is thermodynamically unstable with respect to the isomeric nitrile structure, although isomerization does not usually take place without strong heating (140–250°). In the gas phase, direct isomerization to nitriles is a smooth, first-order process, unaffected by surface catalysis, but accelerated somewhat by *tert*-butyl peroxide.^{54a} Isocyanides are generally unstable to storage, but for a different reason; they usually resinify, on rare occasions explosively, especially when in contact with heavy metal salts. Trimers are formed ordinarily^{54b}; these can explode if heated strongly, but on careful heating they break up to give nitrile (Eq. 63). Phenyl



isocyanide has been reported^{54c} to form a dimer, mp 135°. The revolting stench of isocyanides is legendary.

C. Reactions

Isocyanides react with most heavy metal salts to form very stable complexes, and will even displace carbon monoxide from metal carbonyls to form nonionic complexes of the so-called "zero-valent" metal⁵⁵ (Eq. 64). The complex with cuprous copper is much more stable than that



with cupric, so that cupric salts are much better oxidizing agents in the presence of isocyanides. This is the basis of a convenient and sensitive test for isocyanides whose presence is not otherwise distressingly obvious; benzidine is oxidized to benzidine blue by cupric salts when isocyanides are added (Sievert-Hermsdorf test).⁵⁶

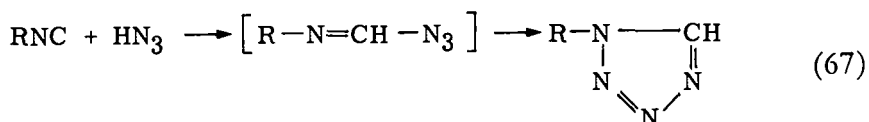
Anhydrous acids form addition products, formimidoyl derivatives (Eq. 65), with isocyanides, while aqueous mineral acid brings about



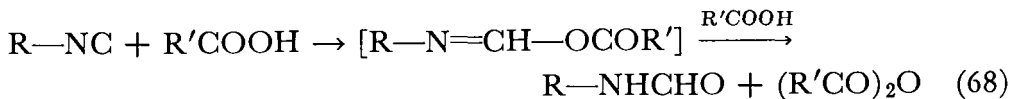
hydrolysis to a primary amine and formic acid (Eq. 66); formamides are



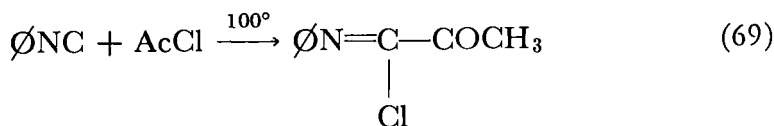
the intermediate stage. Hydrogen azide evidently adds analogously, but the resulting formimidoyl azide cyclizes spontaneously, and 1-substituted tetrazoles are isolated (Eq. 67). Carboxylic acids hydrate iso-



nitriles to formamides, becoming themselves converted to anhydrides (CO in the case of formic acid)⁵⁷ (Eq. 68). The first step here is also undoubtedly 1,1-addition to the isocyanide carbon. With acid chlorides,

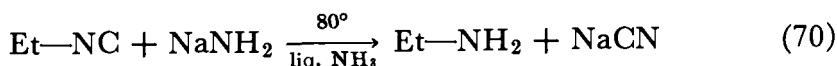


the imidoyl chlorides of α -keto acids are formed (Eq. 69); hydrolysis gives

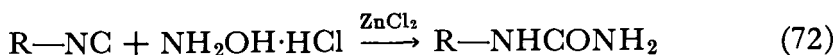
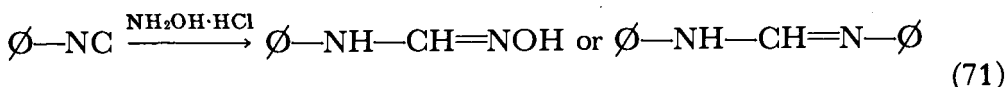


the corresponding α -keto amide.⁵⁸ Sodium amide in liquid ammonia has been found to cleave isocyanides with the formation of primary amine

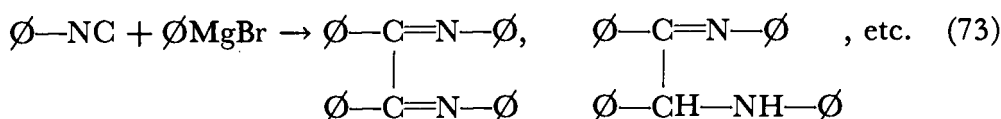
and sodium cyanide ⁵⁹ (Eq. 70), even though isocyanides are inert to hot,



aqueous alkali. Hydroxylamine hydrochloride, however, converts isocyanides to either formamidoximes, formamidines, or ureas, depending on conditions ⁶⁰ (Eqs. 71, 72). Grignard reagents, on the other hand, do

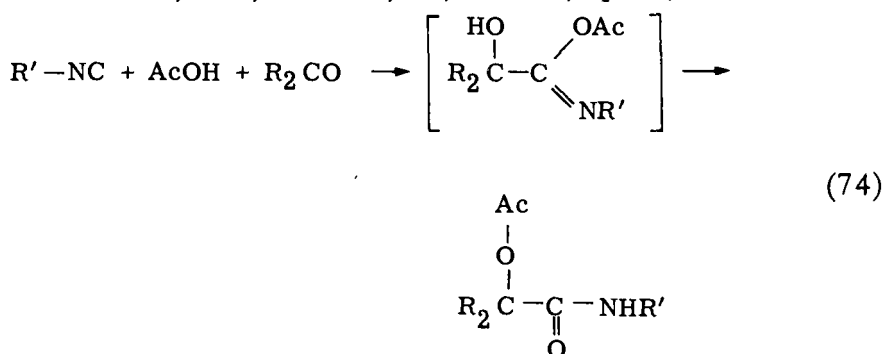


not act in these ways, but give either tars, or dimeric products that appear to arise by addition of RMgX to the isocyanide carbon, followed by oxidation-reduction reactions ⁶¹ (Eq. 73); only traces of aldimines, which



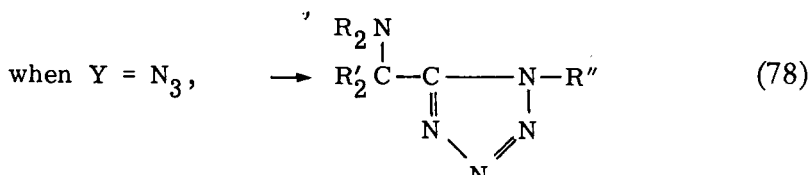
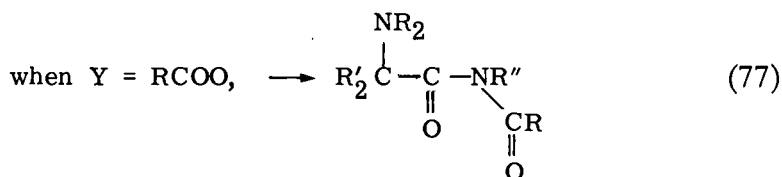
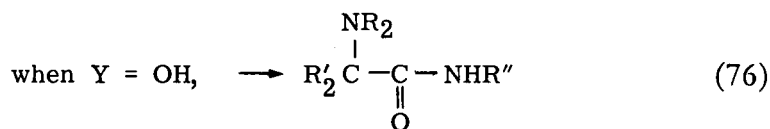
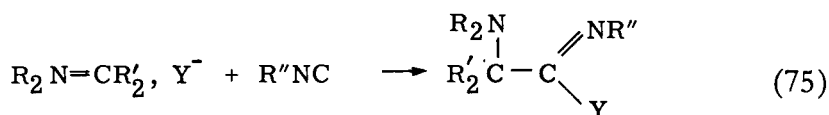
should arise from simple addition, are formed.

Isocyanides do not react with alkylating agents, but they react readily with aldehydes and ketones, especially in the presence of carboxylic acids, giving amides of α -hydroxy or α -acyloxy acids (Eq. 74). This is the

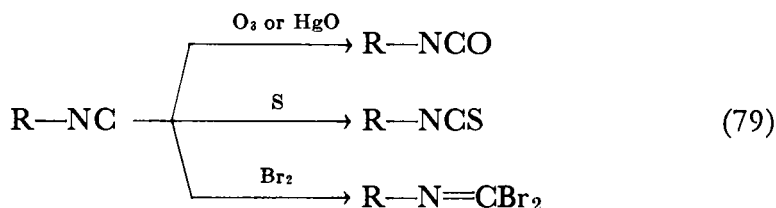


Passerini reaction, and is essentially the reverse of the fission that sometimes occurs in attempted Beckmann rearrangement of α -hydroxy oximes (see Chapter 8). A new carbon-carbon bond is formed between the nucleophilic isocyanide and the electrophilic carbonyl carbon. A mixed anhydride structure is a probable intermediate stage. ⁶²

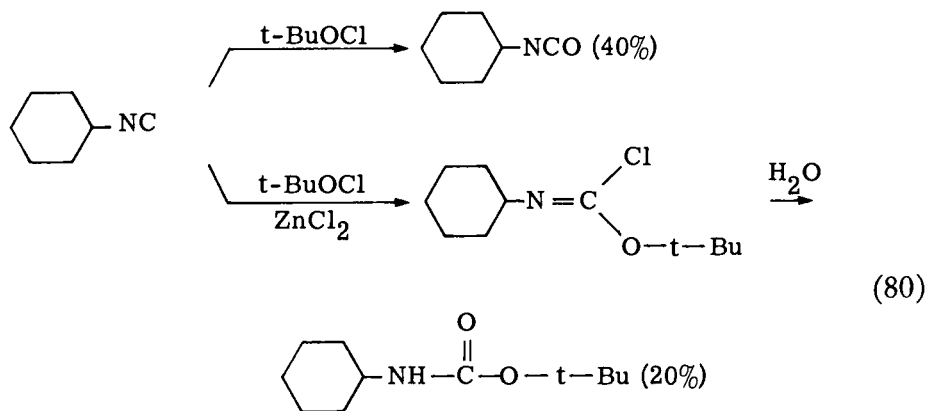
Closely related to the Passerini reaction are the addition reactions of isocyanides to immonium salts ⁶³ (Eqs. 75–78). The electrophilic immonium carbon attacks the isocyanide carbon, to which the anion necessarily present then also becomes attached, forming β -aminoacetimidoyl derivatives. Depending on the nature of the anion taken up, these products often then tautomerize, cyclize, or rearrange.



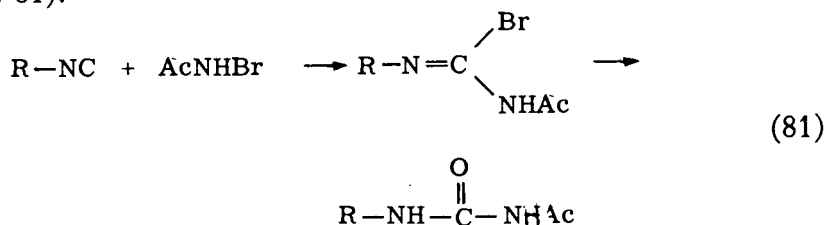
Oxidizing agents readily attack the carbon of isocyanides, giving either isocyanates or addition compounds with the oxidizing agent ⁶⁴ (Eq. 79). Even dimethyl sulfoxide functions as an oxidizing agent toward



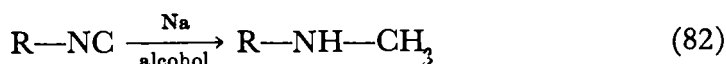
isocyanides if a trace of bromine is present as a catalyst.^{64d} *Tert*-butyl hypochlorite by itself oxidizes isocyanides to isocyanates, but in the presence of zinc chloride it simply adds to produce carbonimidoyl chlorides; water hydrolyzes these to urethans ^{60b} (Eq. 80). *N*-Bromo amides



also add; the products, guanyl bromides, are easily hydrolyzed to acyl ureas ^{60b} (Eq. 81).

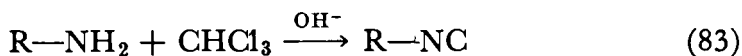


Reduction with various reagents, such as sodium and alcohol, converts isocyanides to secondary methylamines ⁵⁸ (Eq. 82).

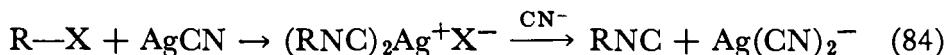


D. Preparation

The reaction of chloroform with primary amines in the presence of hot alkali has been discussed in Chapter 2; it is commonly considered as a qualitative test for primary amines, but it can also be used as a preparative method ^{63, 66} (Eq. 83). Alkylation of heavy metal cyanides,



particularly copper and silver, gives isocyanides in preparatively useful yields.⁶⁶ The isocyanides are not produced directly, but must be released from the metal complex compounds first formed, potassium cyanide being the best reagent (Eq. 84).

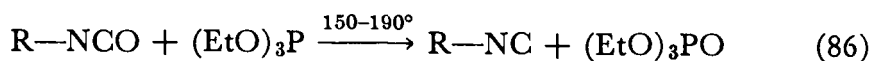


The dehydration of N-substituted formamides (Eq. 85) has been

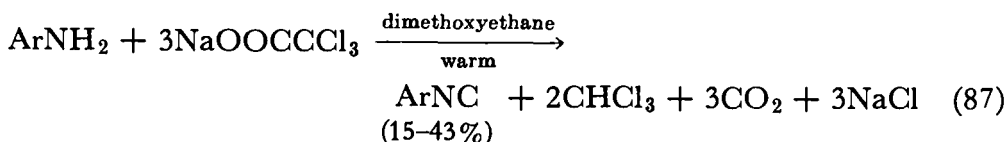


introduced as a preparative method much more recently.⁶⁷ Acid halides, such as toluenesulfonyl chloride, phosphoryl chloride, or phosgene are used in the presence of a base, such as a tertiary amine or potassium *tert*-butoxide. The method is applicable to both aliphatic and aromatic compounds, and yields are usually good. A somewhat similar reaction is the removal of hydrogen sulfide from thioformamides by means of heavy metal oxides (Chapter 4).

A new and therefore little-tried preparation of isocyanides is the deoxygenation of isocyanates with alkyl phosphites ⁶⁸ (Eq. 86). It appears



to be best suited for alkyl isocyanides, where yields have run from 34 to 57%. Another recent innovation is the preparation of isocyanides by the decomposition of sodium trichloroacetate in the presence of amines⁶⁹; this reaction is presumed to involve dichloromethylene, CCl_2 , similar to the chloroform-amine reaction (Eq. 87).



The Beckmann fission, by which certain oximes are converted in part to isocyanides, is not usually considered to be of preparative importance (Chapter 8).

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*chapter
six*

Nitrogen Derivatives of Carbonic Acid

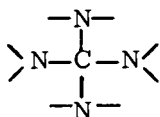
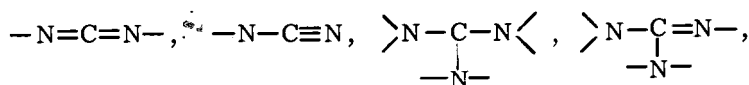
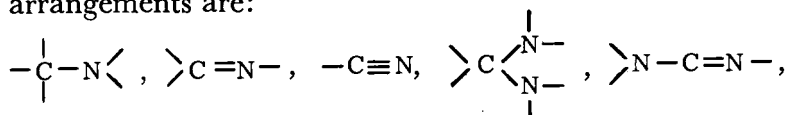
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INTRODUCTION

The chemistry of nitrogen derivatives of carbonic acid is considerably more involved than that of other organic acids and on that basis alone might merit treatment in a separate chapter. However, there is the additional factor that some of the structures that appear to be merely a combination of two simpler functions whose properties have already been discussed, behave, in reality, as new and distinct functional groups. Thiocyanates, $R-SCN$, for example, do indeed show many of the properties to be expected of nitriles, but also show additional reactions in which the group $-SCN$ must be considered as a whole.

Because the carbon of carbonic acid is attached to no hydrogen or other carbon, all of its bonds are potentially attachable to nitrogen. This

situation leads not only to compounds having one, two, three, or four bonds from the same carbon to nitrogen, but also to the possibility of various combinations of single, double, and triple bonds. The formally possible arrangements are:



Most of these ten classes of compounds are important. To be considered derivatives of carbonic acid, compounds corresponding to these structures must have the remaining bonds of the carbonic acid carbon attached to some atom other than carbon or hydrogen, of course; in this chapter, only compounds having attachment to oxygen or sulfur will be considered.

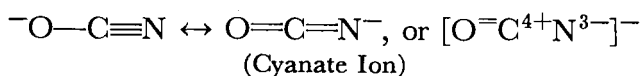
Since the chemical behavior is strongly influenced by the coordination number of the central carbon, i.e., the total number of atoms attached to it, the primary division in this chapter is made on this basis, followed by a subdivision according to the number of nitrogen atoms. Derivatives of carbonic acid that are also derivatives of hydroxylamine or hydrazine, as, for example, semicarbazide, are discussed in the chapters devoted to the corresponding classes of nitrogen compounds.

COMPOUNDS WITH DICOÖRDINATE CARBON

A. Cyanic and Thiocyanic Acid Derivatives

NOMENCLATURE AND GENERAL Cyanic and thiocyanic acids are tautomeric substances, capable of existing as $\text{H}-\text{O}-\text{C}\equiv\text{N}$ or $\text{O}=\text{C}=\text{NH}$, and $\text{H}-\text{S}-\text{C}\equiv\text{N}$ or $\text{S}=\text{C}=\text{NH}$. Although the separate tautomers have not so far been isolated, they can be detected in equilibrium with each other by spectroscopic means, and organic derivatives of both bond arrangements are well known. For purposes of nomenclature, the tautomers with triple bonds are considered to correspond to the ordinary name for the acids, whereas the tautomers with cumulative double bonds (allene structure) are referred to as isocyanic and isothiocyanic acid. The equilibrium mixtures of the tautomers, as they would exist in a water solution of the acids, for example, are referred to by the names without the

“iso” prefix. The anions from either tautomer are identical, of course, and are called “cyanate” or “thiocyanate.” Such a term as “isocyanate ion” is meaningless; the iso- prefix is used only to distinguish covalently bonded isomers. It should be mentioned that there is a pair of tautomers isomeric with cyanic acid that also give rise to organic derivatives: fulminic



acid, H—O—NC or ONCH . These are hydroxylamine derivatives, and are discussed in Chapter 8.

Derivatives of cyanic and thiocyanic acid are named as though they were esters, which formally they are. The names thus consist of two words, as “ethyl isocyanate” ($\text{C}_2\text{H}_5\text{NCO}$) and “phenyl thiocyanate” ($\text{C}_6\text{H}_5\text{SCN}$). In *Chemical Abstracts*, these compounds are listed as esters, under the name of the specific tautomeric form of the parent acid; i.e., thiocyanates are listed under thiocyanic acid, isothiocyanates under isothiocyanic acid. When it is necessary to name these functions as prefixes, the forms are “isocyanato-”, “thiocyanato-”, etc.; the “-at-” in these prefixes is essential, since “isocyano-” means “ CN^- ”.

In the older literature, particularly the German, thiocyanates are often called “rhodanides,” after an old name for thiocyanic acid; the term “sulfocyanide” is also sometimes encountered. The expression “mustard oil” (German “Senföl”) was once common for isothiocyanates, and is still occasionally used. It derives from the fact that allyl isothiocyanate, the earliest recognized example, is obtained from mustard seed.

PROPERTIES The smaller cyanates, isocyanates, isothiocyanates, and thiocyanates are all liquids.¹ Neopentyl cyanate boils at 123° , phenyl at $75^\circ/10\text{ mm}$. Isothiocyanates naturally boil at higher temperatures than isocyanates, owing to their higher molecular weight, as illustrated by methyl isocyanate, bp 44° , and methyl isothiocyanate, bp 117° . Thiocyanates (RSCN) boil 10 to 15° higher than isothiocyanates (RNCS). The boiling points of isocyanates lie well above those of the hydrocarbons of similar molecular weight, showing that there is an appreciable dipole within the group; however, isocyanates still boil far below the analogous nitro compounds (cf. phenyl isocyanate, bp 165° ; isopropylbenzene, bp 150° ; nitrobenzene, bp 210°). Even the smallest members of these groups are hardly soluble in water. Isocyanates are unbearable lachrymators, but the isothiocyanates are merely mild inflammatory agents; the odor of the latter reminds one of a good sausage, and in small amounts they are flavoring agents.

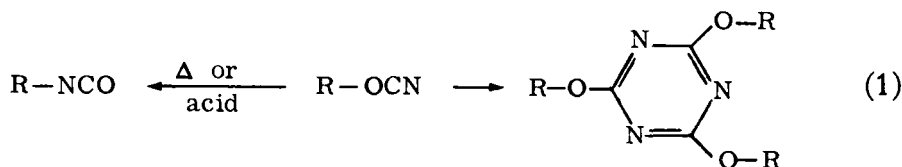
All members of these groups are essentially nonbasic in comparison to water, although they are undoubtedly protonated (and subsequently hydrolyzed) by concentrated mineral acids. The parent compounds

cyanic and thiocyanic acid are moderately strong acids, HNCO having an ionization constant ² of 3.4×10^{-4} , and HNCS being considerably stronger, as is to be expected of a sulfur analogue (cf. H_2S vs. H_2O). Both are quite volatile, and both decompose in the free state, whether undiluted or in solution (thiocyanic acid solutions can be kept longer than cyanic acid, which is a mild explosive, but can be kept for months at -50°).^{2b}

All members of these groups show infrared absorption in the region common to triple bonds and cumulative double bonds: most isocyanates ³ absorb near 2270 cm.^{-1} , isothiocyanates ⁴ at $2060\text{--}2105 \text{ cm.}^{-1}$, acyl isothiocyanates at 1960 cm.^{-1} , and thiocyanates near 2140 cm.^{-1} . Isocyanates have little absorption in the near ultraviolet. The N—C—O and N—C—S atoms lie along a straight-line axis in both the ions and organic derivatives; substituents are attached at an angle to the axis, at whichever end.

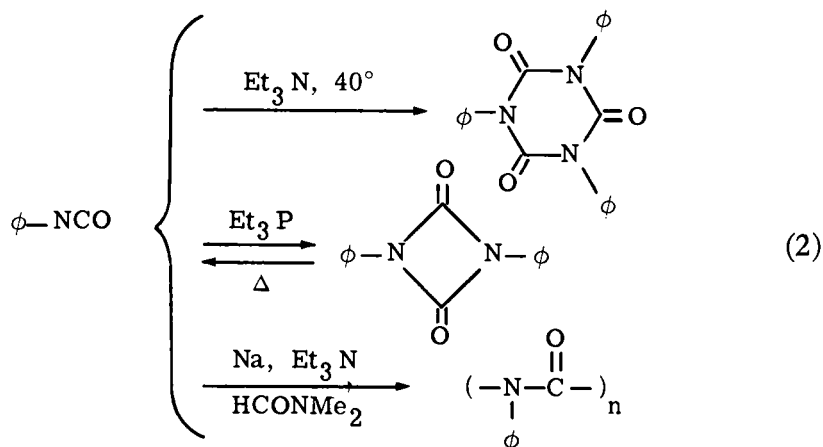
REACTIONS ⁵ The chemistry of cyanates and isocyanates is dominated by polymerization and by addition of nucleophiles having an active hydrogen. The sulfur analogues do not polymerize readily, but attack by nucleophiles is also their most characteristic reaction, although their reactivity is noticeably less.

Polymerization usually leads to cyclic trimers,⁶ derivatives of 1,3,5-triazine, although dimers and linear high polymers may also be formed. Trimerization of cyanates occurs so readily that until recently no monomer had ever been isolated; only hindered ones,⁷ such as neopentyl and 2,6-di-*tert*-butylphenyl cyanates, are stable. Trimerization produces cyanurate esters; contact with acids, such as boron fluoride etherate, catalyzes rearrangement of alkyl cyanates to isocyanates (Eq. 1).⁷

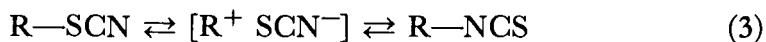


Isocyanates are usually stable to storage when pure, but salts and tertiary amines catalyze trimerization; isocyanurates are formed (Eq. 2). A reversible dimerization of phenyl isocyanate to a four-membered-ring compound,⁸ 1,3-diphenyluretidinedione, is brought about by triethylphosphine. A linear polymer ⁹ is formed by contact with sodium dispersed in dimethylformamide containing triethylamine. Cyanic acid itself also polymerizes, forming cyanuric acid (2,4,6-trihydroxy-*sym*-triazine) and "cyamelide," believed to be a linear polymer ¹⁰ (Eq. 2).

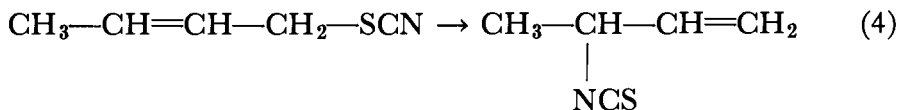
Isothiocyanates are nearly free of the tendency to polymerize characteristic of the oxygen analogues ¹¹; an acid-catalyzed trimerization of



alkyl thiocyanates has been reported, however. Isothiocyanates are stable to heat and prolonged storage, but many thiocyanates rearrange slowly to isothiocyanates.¹² It appears that isothiocyanates are always thermodynamically more stable than the corresponding thiocyanates, differences of 9 to 17 kcal/mole having been found from measurements of heats of combustion¹³; only when the structure of the group attached to sulfur is suitable is the arrangement fast enough to be significant. The principal path is ionization and recombination (Eq. 3), and accordingly,

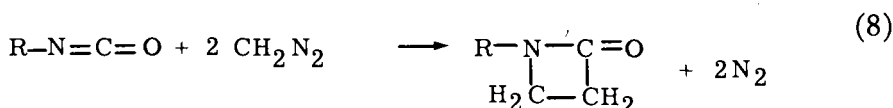
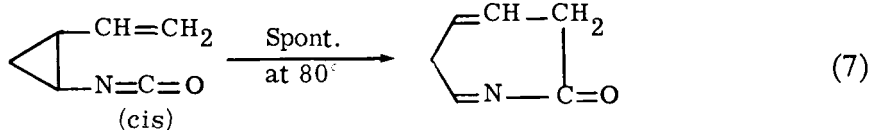
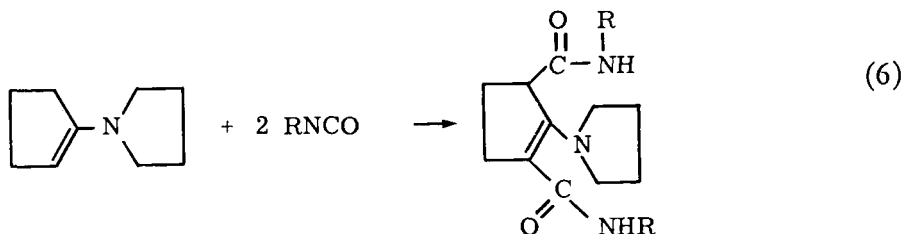
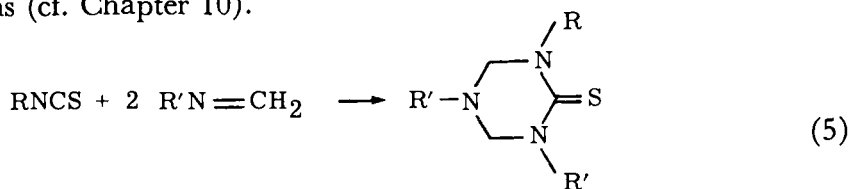


only groups that have significant stability as cations can thus migrate in such a manner from sulfur to nitrogen. Anhydrous zinc chloride is a catalyst for the reaction. Tertiary alkyl and benzyl thiocyanates will rearrange, but primary alkyl thiocyanates are quite inert (except methyl thiocyanate). Groups with especially great ability to form carbonium ions, such as acyl and triarylmethyl, rearrange so readily that only the isothiocyanates have been obtained pure. Allyl thiocyanates rearrange by a cyclic path, which can also entail position isomerism (Eq. 4).

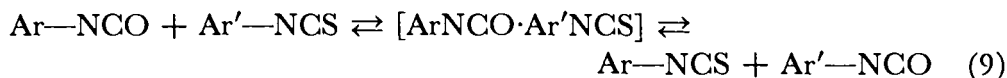


Isocyanates and isothiocyanates will in some cases undergo addition with other unsaturated structures, such as formaldimines, enamines,¹⁴ diazoalkanes,¹⁵ and olefinic unsaturation in the same molecule¹⁶ (Eqs. 5–8). The case of *cis*-2-vinylcyclopropyl isocyanate¹⁶ (Eq. 7) is an example of valence isomerism corresponding to the Cope rearrangement in cyclooctatetraene chemistry. This isocyanate is converted to an azepinone as soon as it is formed, whereas the *trans* isomer is stable. The

addition of diazomethane to isocyanates constitutes an important synthesis of β -lactams (cf. Chapter 10).



The equilibration between aryl isocyanates and isothiocyanates,¹⁷ amounting to an exchange of groups, may actually also be an addition reaction, in which an unstable adduct can dissociate in either of two ways (Eq. 9).



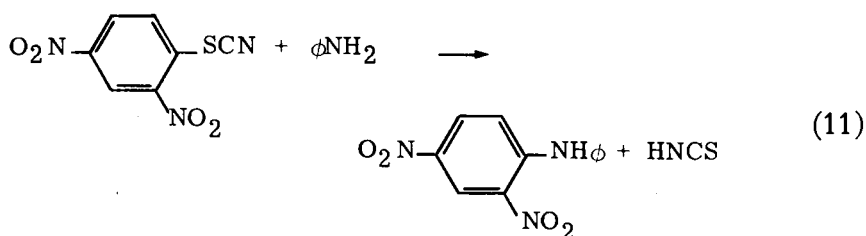
The carbon atom of isocyanates and isothiocyanates is evidently a strongly positive center and adds nucleophiles readily. Thiocyanates, in contrast, are relatively inert; alkyl thiocyanates usually behave as weak alkylating agents toward nucleophiles. Methyl, ethyl, and benzyl thiocyanates, for example, react with trimethylamine to give quaternary ammonium thiocyanates¹⁸ (Eq. 10), and *tert*-butyl thiocyanate reacts with



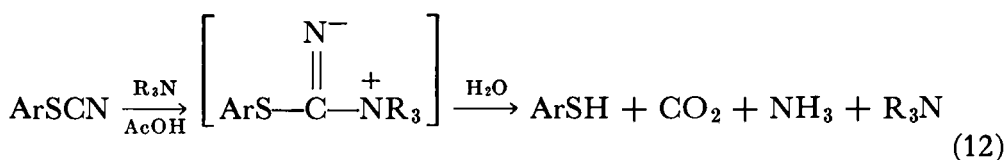
phenol in the presence of zinc chloride to give some *p-tert*-butylphenol.^{12a}

Aryl thiocyanates act as arylating agents only when strongly activated by electron-withdrawing substituents, as in the case of 2,4-dinitrophenyl

thiocyanate, which reacts with aniline to give 2,4-dinitrodiphenylamine¹⁹ (Eq. 11). Aryl thiocyanates that cannot readily undergo such displace-

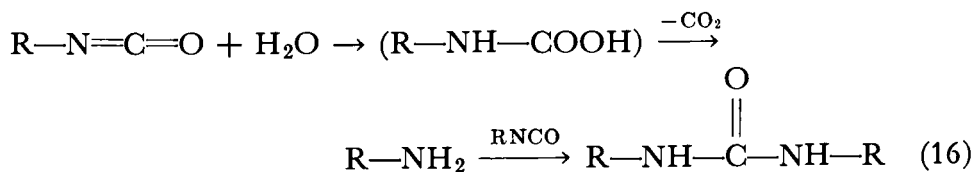
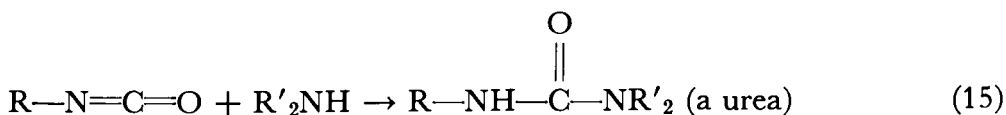
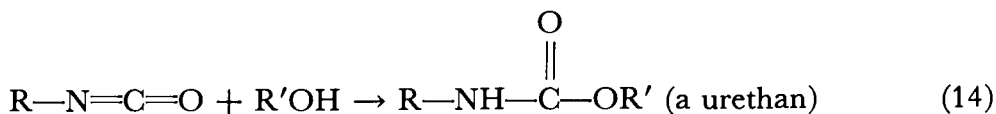


ment react in the presence of amines in a quite different way, apparently involving attack at the thiocyanate carbon, when heated in acetic acid containing a trace of water. Diaryl disulfides are produced cleanly, in nearly quantitative yields, and the amine, recovered unchanged, plays the role of a catalyst.²⁰ The oxidation of the sulfur portion of the thiocyanate group is not caused by air acting on a mercaptan first formed, but is accounted for by conversion of half of the cyano moiety to hydrogen cyanide (Eqs. 12, 13). The actual oxidation-reduction step is between



a mole of mercaptan and one of thiocyanate, and can be carried out independently; it is perhaps a case of nucleophilic displacement on the thiocyanate sulfur.

The addition of nucleophiles derived from active hydrogen compounds, such as water,²¹ alcohols, mercaptans,²² amines, amides, etc. (Eqs. 14–16),



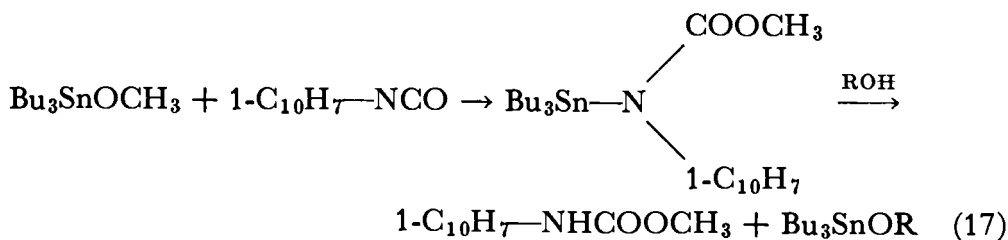
to isocyanates occurs in most cases spontaneously with evolution of heat. The products are carbamic acid derivatives: ureas, urethans, etc. The

polyurethan polymers are obtained in this way from diisocyanates and polyols.⁵ The reaction with water gives a symmetrical urea as an end product^{21a}; carbamic acids, which must be formed first, are known to decarboxylate spontaneously, and the resulting amine reacts with more isocyanate. Because of the ease of the reaction, even with the moisture of the air, isocyanates must be tightly sealed when stored.

Hydrolysis is catalyzed by both acid and base; in the latter case, the reaction can sometimes be stopped at the stage of simple addition of OH^- , which gives a carbamate salt.^{21b}

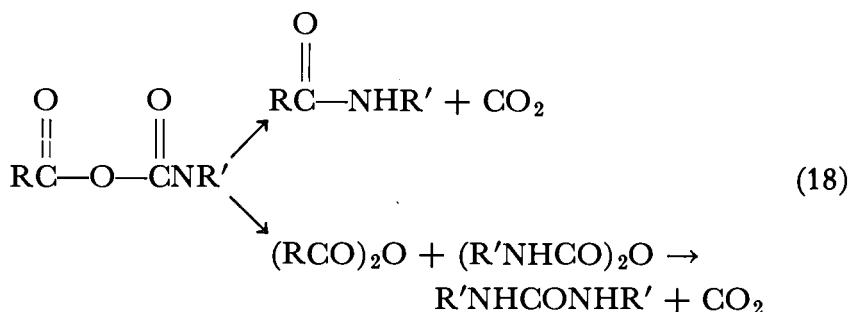
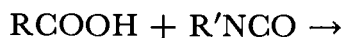
The reaction of isocyanates with alcohols is a 1:1 addition to give urethan, but the simple stoichiometry is deceptive. The kinetics of the reaction have been studied intensively because of its industrial importance. Reaction usually occurs readily enough on warming, but it is subject to catalysis by a wide and seemingly unrelated variety of substances, particularly amines, and including urethans, so that the reaction is mildly autocatalytic. By far the most effective catalyst is dibutyltin dilaurate, which is used industrially. Since some amines are ineffective, and some active catalysts are not proton acceptors, catalysis is believed not to entail conversion of the alcohol to its more strongly nucleophilic anion, but to occur through an as yet incompletely elucidated complex formation with the isocyanate moiety.^{5, 13}

The path through which organotin compounds act as catalysts appears to have been elucidated in the example of tributyltin methoxide, which reacts rapidly with α -naphthyl isocyanate to form an addition compound that reacts rapidly with alcohols to regenerate a tributyltin alkoxide^{23d} (Eq. 17).

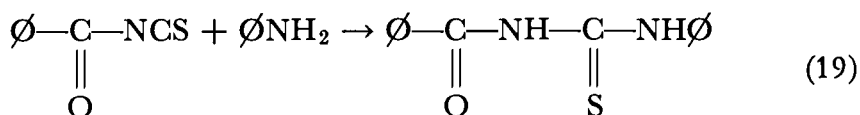


The reactivity of aryl isocyanates toward alcohols is enhanced by electron-withdrawing substituents, and follows the Hammett linear free energy relationship²⁴ with a value of $\rho = 1.69$. The reactivity toward amines shows a parallel influence.²⁵

Carboxylic acids give mixed anhydrides, which easily lose carbon dioxide to form amides or disproportionate to symmetrical anhydrides, eventually giving symmetrical ureas²⁶ (Eq. 18). With aliphatic acids, the first reaction predominates, whereas aromatic acids react mostly by the second path.

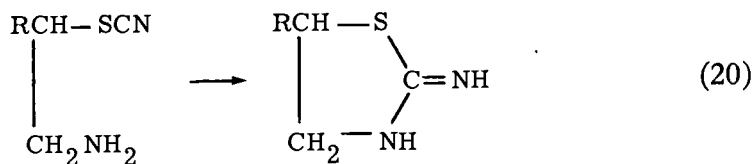


Although isothiocyanates react with nucleophiles in general in the same way as do isocyanates, they are sluggish in comparison. Weakly basic amino groups, such as those of amides, are not attacked, unless their nucleophilicity is increased by conversion to an anion,²⁷ e.g., RSO_2NH^- . Isothiocyanates are inert to water, and even catalyzed hydrolysis is usually slow, requiring hours of refluxing with strong acid. Electron withdrawal enhances the electrophilic reactivity of the isocyano group noticeably; this influence reaches a maximum in acyl isothiocyanates, which are so reactive that even feebly basic amines are converted rapidly to thioureas by them²⁸ (Eq. 19). The other extreme of reactivity toward



nucleophiles is perhaps represented by the thiocyanate ion; ammonium thiocyanates are converted only slowly to thioureas by heating, and usually incompletely.

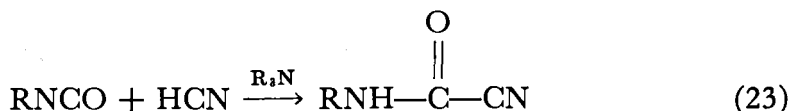
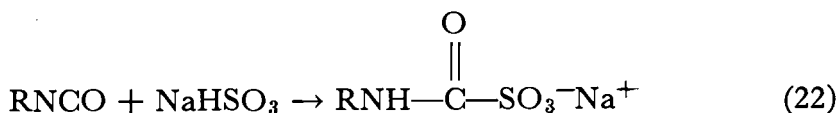
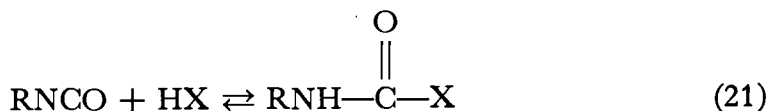
The difference in reactivity toward nucleophiles shown between thiocyanates and isothiocyanates is one of both degree and kind, and is sufficiently sharp to allow a quantitative determination of the more reactive isothiocyanate by treatment with excess primary amine, and back titration of the excess amine with standard acid.²⁹ Only when ring formation is involved do amino groups add readily to thiocyano groups³⁰ (Eq. 20).



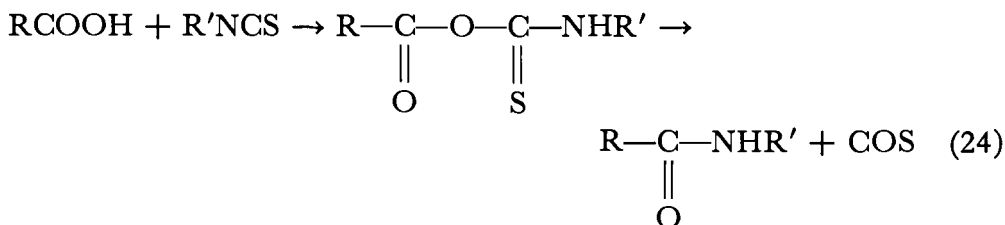
A qualitative test to distinguish between thiocyanates and isothiocyanates has been proposed on the basis of a reaction with sodium azide and

dimethylformamide ³¹; isothiocyanates give a pronounced effervescence, whereas thiocyanates are inert.

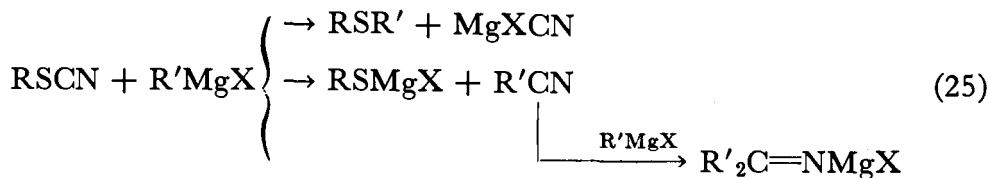
Distinctly acidic substances, such as hydrogen halides, sodium bisulfite, and hydrogen cyanide, add to isocyanates and isothiocyanates to form carbamyl derivatives that are particularly easily dissociated into the starting materials ³² (Eqs. 21–23). Even though acidic conditions may



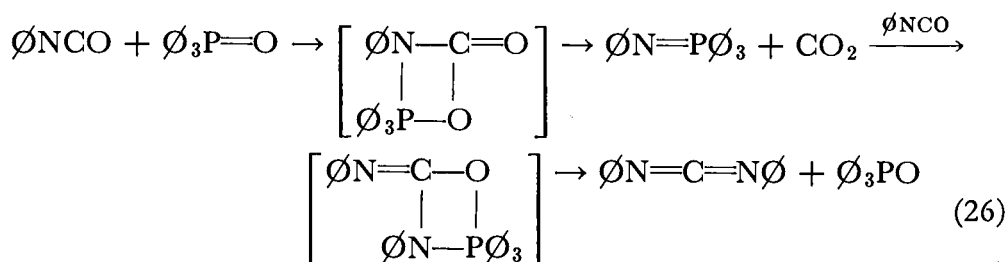
obtain, the formation of these products still may involve attack by the anion; indeed, the addition of hydrogen cyanide requires a basic catalyst. Carboxylic acids react with isothiocyanates to give amides and carbon oxysulfide, analogous to the reaction with isocyanates ^{26a} (Eq. 24).



Potential carbanions, such as the sodio derivatives of active methylene compounds, ³³ and organometallic reagents, ³⁴ add to isocyanates and isothiocyanates in the same way as other nucleophiles. The products, amides or thionamides, are obtained in preparatively useful yield. Thiocyanates, however, act as sources of a cyano group by attack at the carbon, or sources of the R—S— group by attack on sulfur ³⁵ (Eq. 25).

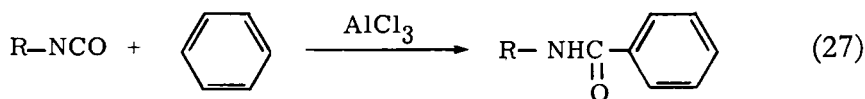


Certain oxides with semipolar structure, particularly phosphine oxides, act as catalysts for the disproportionation of isocyanates to carbodiimides and carbon dioxide ³⁶ (Eq. 26). The "catalysts" probably attack the



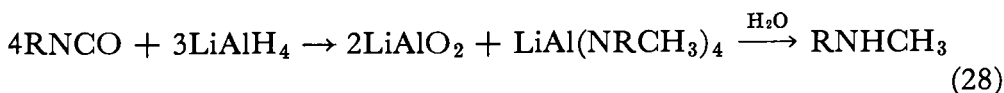
electrophilic isocyanate carbon atom first, leading to imines, such as $\text{R}_3\text{P}=\text{NR}'$, which attack a second isocyanate molecule. Yields as high as 88% have been reported. Isothiocyanates react similarly but in very poor yield.

In the presence of Lewis acids, such as aluminum chloride, isocyanates and isothiocyanates are converted into powerful electrophiles, capable of attacking aromatic rings. N-Substituted benzamides or benzthionamides are produced ³⁷ (Eq. 27); since these can usually be hydrolyzed to the

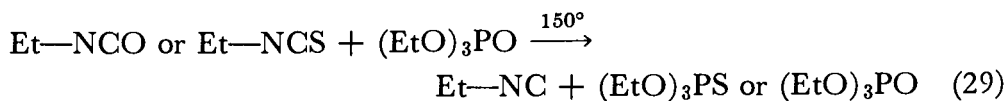


corresponding benzoic acids, the over-all process amounts to carboxylation of the aromatic ring, and is a useful synthetic method.

The only practical reduction of isocyanates and isothiocyanates appears to be by lithium aluminum hydride (Eq. 28), which leads to

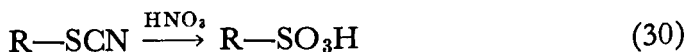


secondary amines by converting the carbonyl group to a methyl.³⁸ However, desulfuration or deoxygenation to give isocyanides can be accomplished with triethyl phosphite ³⁹ (Eq. 29). Isocyanates are inert

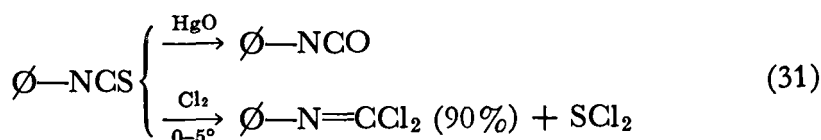


to oxidation unless the conditions chosen are severe enough to attack the substituent group. On the other hand, the sulfur in both thiocyanates

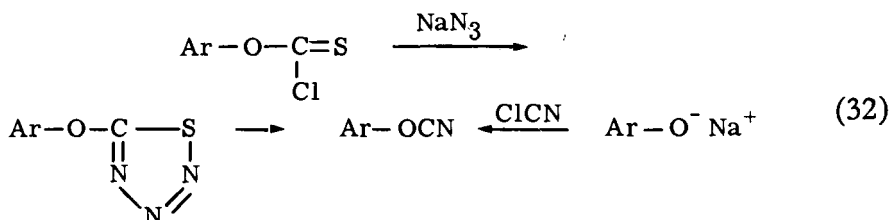
and isothiocyanates is in the reduced state, and is thus susceptible to oxidative attack. Thiocyanates yield sulfonic acids (Eq. 30), and iso-



thiocyanates have their sulfur replaced by halogen or oxygen, giving isocyanates or carbonimidoyl dihalides (Eq. 31).⁴⁰

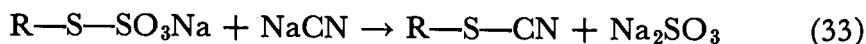


PREPARATION ⁵ *Cyanates* Both alkyl and aryl cyanates have been prepared by the reaction of alkoxides or phenoxides with cyanogen chloride,⁷ but when this reaction is applied to unhindered systems, the products trimerize before they can be isolated. Phenyl cyanate has been prepared by the spontaneous decomposition of 5-phenoxy-1,2,3,4-thiatriazole (Eq. 32). Thiocyanates, however, can be prepared in wide variety

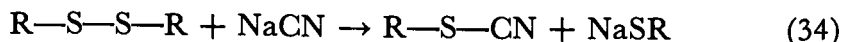


by the reaction of cyanogen chloride with mercaptides,⁴¹ although this is not a preferred preparative method.

Thiocyanates Thiocyanates are prepared more conveniently by the reaction of alkyl thiosulfates, obtained from alkylating agents and sodium thiosulfate, with sodium cyanide ^{42a} (Eq. 33). Dialkyl disulfides react



similarly ^{42b} (Eq. 34). These reactions are apparently cases of nucleo-

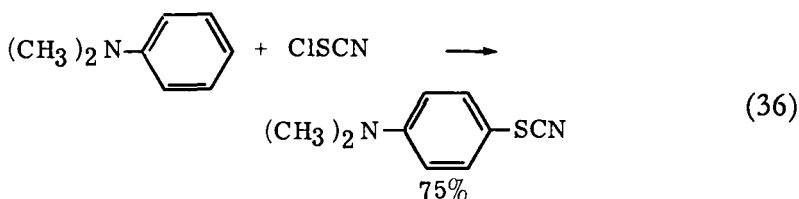


philic displacement on a sulfur atom. Alkylation of thiocyanate salts takes place principally on sulfur, the more nucleophilic site, giving alkyl thiocyanates; it constitutes a feasible synthetic method even for tertiary

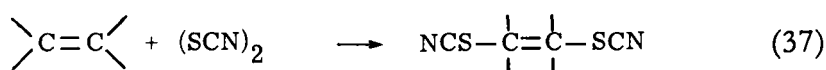
alkyl thiocyanates if suitable conditions are chosen.⁴³ The reason for this success with tertiary alkyl chlorides may be that, although thiocyanate ion is a good nucleophile, its base strength is quite low, so that it does not promote the base-catalyzed elimination that predominates with most nucleophiles. Thiocyanogen and its chloride, $\text{Cl}-\text{SCN}$, can be used to



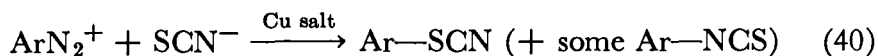
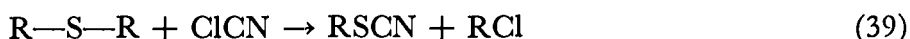
prepare thiocyanates in special cases,⁴⁴ such as the thiocyanation of dimethylaniline (Eq. 36), and addition to olefins, which can be deter-



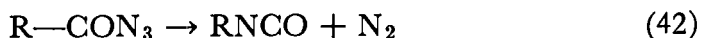
mined quantitatively in this manner (Eq. 37).



Additional reactions of preparative value for thiocyanates are the reaction of sulfonyl chlorides with potassium cyanide,^{45a} the cleavage of dialkyl sulfides with cyanogen chloride,^{45b} and the Sandmeyer-type reaction of diazonium salts with thiocyanate ion in the presence of a copper catalyst^{45c} (Eqs. 38–40).

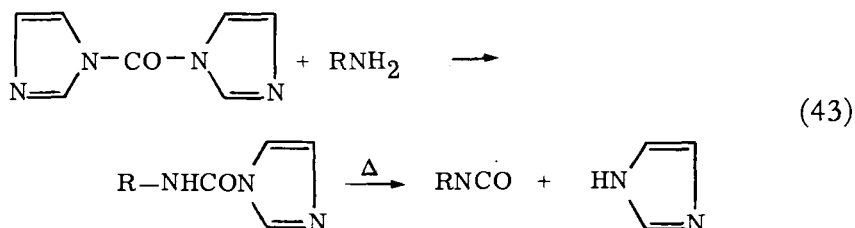


ISOCYANATES Isocyanates are conveniently prepared either by the reaction of primary amines with phosgene⁴⁶ (used industrially), or by the Curtius rearrangement of acyl azides⁴⁷ (see Chapter 10) (Eqs. 41, 42).

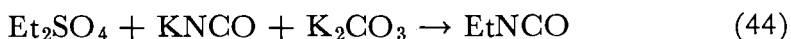


They have also been prepared by the Hofmann and Schmidt rearrangements.⁴⁸ An interesting method that may be general has been introduced recently; carbamyl imidazoles, obtained by the reaction of carbonyl

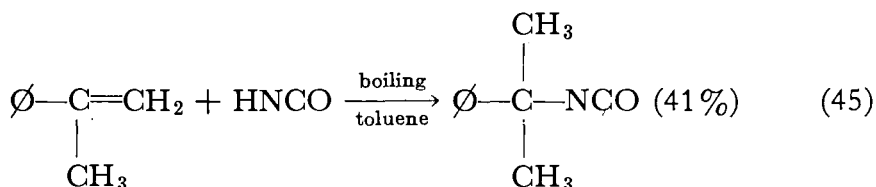
diimidazole with primary amines, dissociate into imidazole and an isocyanate on heating ⁴⁹ (Eq. 43). Although the direct alkylation of cyanate



salts,⁵⁰ such as silver or potassium cyanate, would appear to be a simple route to alkyl isocyanates, it has not been found to be a general method of value, owing to the commonly low yields. Significant exceptions are the preparations of methyl and ethyl isocyanates from the sulfates and potassium cyanate, which have given yields up to 95% (Eq. 44). The

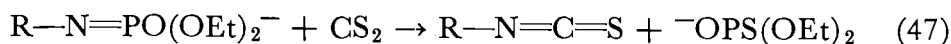
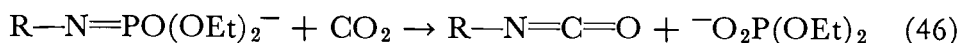


addition of anhydrous cyanic acid to olefins ^{50d} (Eq. 45) may become of

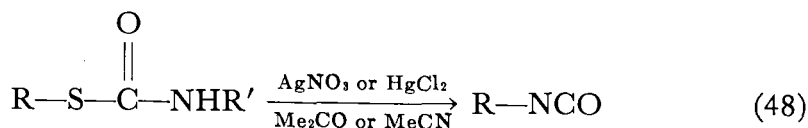


use, but the reaction has not been sufficiently explored.

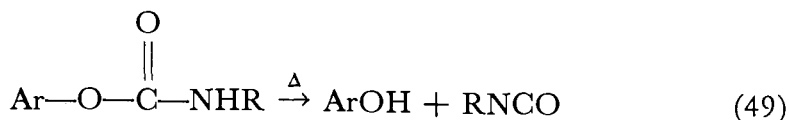
The use of phosphine imine derivatives to synthesize isocyanates or isothiocyanates by reaction with carbon dioxide or carbon disulfide is a recent method of promise ^{36c} (Eqs. 46, 47).



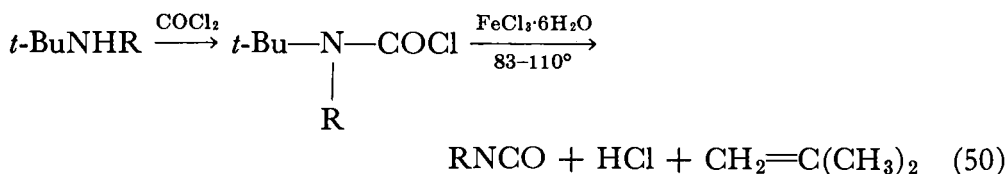
Cleavage of carbamic acid derivatives leads to isocyanates in yields of preparative value in three ways. Thiocarbamates lose mercaptan to silver nitrate or mercuric chloride, leaving isocyanates ^{51a} (Eq. 48).



Pyrolysis of aryl carbamates produces isocyanates by elimination of phenol ^{51b} (Eq. 49). N-Alkyl-N-*tert*-butylcarbamoyl chlorides undergo



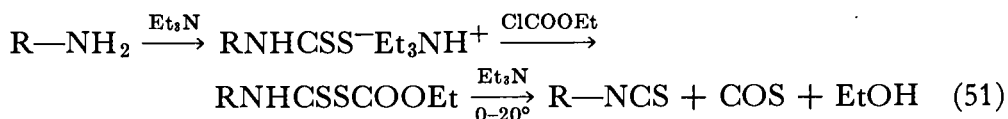
a double elimination on warming to give an isocyanate, isobutene, and hydrogen chloride ^{51c} (Eq. 50); the yields are good, and otherwise in-



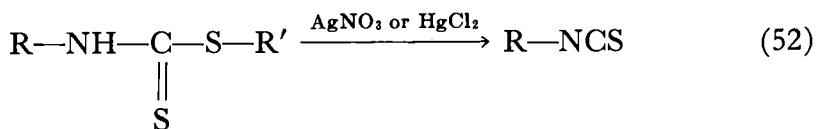
accessible isocyanates can be prepared.

Although the oxidation of isocyanides to isocyanates can be accomplished in good yield, it is not likely to be of synthetic value, owing to the tediousness of preparing the isocyanides (see Chapter 5).

ISOTHIOCYANATES Some isothiocyanates can be prepared by the rearrangement of thiocyanates, but the usefulness of this method is limited.¹² The reaction of thiophosgene, which is troublesome to obtain, with primary amines gives isothiocyanates,⁵² but a better method to convert primary amines to isothiocyanates is the Kaluza reaction.⁵³ In this method, a dithiocarbamate is obtained from a primary amine by reaction with carbon disulfide, and this is made to lose the elements of hydrogen sulfide by one or another indirect route. The most convenient way makes use of the base-catalyzed elimination reaction in a mixed anhydride prepared from the dithiocarbamate salt without isolation (Eq. 51).

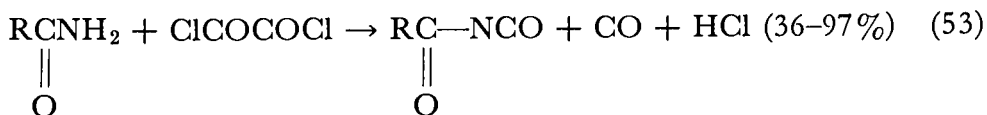


Alternatively, the zinc salt of the carboxymethyl dithiocarbamate can be decomposed at pH 7,⁵⁴ or the alkyl dithiocarbamate can be made to lose mercaptan by reaction with silver nitrate or mercuric chloride ^{51a} (Eq. 52).

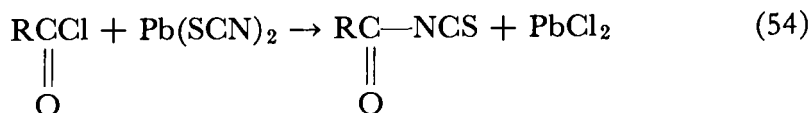


Other synthetic methods, such as the addition of sulfur to isocyanides, the spontaneous decomposition of thioxazolines,⁵⁵ and the cleavage of thioureas by heat, acid, or acetic anhydride,⁵⁶ are of less general importance.

Acyl isocyanates are conveniently prepared by the reaction of amides with oxalyl chloride ⁵⁷ (Eq. 53), and acyl isothiocyanates by the reaction



of acyl chlorides with lead thiocyanate ⁵⁸ (Eq. 54).



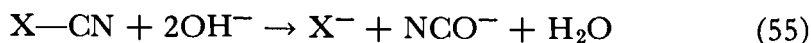
B. Halogen Cyanides and Related Pseudohalogens

The compounds X-CN are the acid halides of cyanic acid, and one might reasonably suppose that they should be named accordingly, as "cyanyl halides." They are, however, most frequently called "cyanogen halides," occasionally "halogen cyanides." The substance $(\text{SCN})_2$ is called "thiocyanogen," a name that is convenient, but gives no clue that its structure is $\text{N}\equiv\text{C-S-S-C}\equiv\text{N}$. Cyanogen⁵⁹ (oxalonitrile), NC-CN , although technically not related, shows many similarities to the other pseudohalogens.

The cyanogen halides are useful but highly toxic compounds and have a biting odor. They are all quite colorless, and all are extremely volatile. The fluoride and chloride are gases, whereas the bromide and iodide are solids, mp 52° and 146.5° , respectively, that sublime very readily (BrCN boils at 61.5°). Because of the combination of toxicity and volatility, it is recommended that a gas mask be used when working with the chloride or bromide. Thiocyanogen is an unstable substance that forms colorless crystals, mp -3° .

Although the cyanogen halides can easily be stored for decades, they polymerize to cyanuryl halides (2,4,6-trihalo-*sym*-triazines) in the presence of impurities, in a manner analogous to cyanic acid and cyanates.

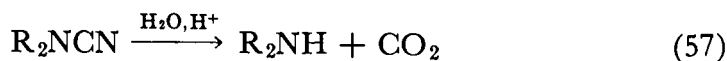
The main reactions of the cyanogen halides are those to be expected of acid halides; they act as "cyanylating" agents toward nucleophiles. Although they are stable to water alone, a base hydrolyzes them to halide and cyanate (Eq. 55). Amines are converted to cyanamides, a useful



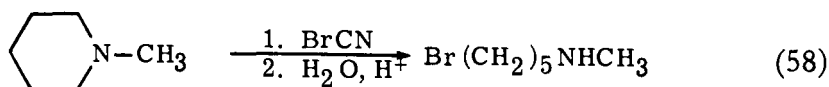
preparative method⁶⁰ (Eq. 56). Even tertiary amines react; the initially



formed N-cyano quaternary salts, $\text{R}_3\text{N}^+-\text{CN X}^-$, break up spontaneously or on warming into a dialkylcyanamide and an alkyl halide, one of the several reactions bearing the name "von Braun."⁶¹ It is a method of value in degradative structure determination; the dialkyl cyanamides can readily be hydrolyzed to more easily identifiable secondary amines (Eq. 57). The reaction can be used to open rings, as in the

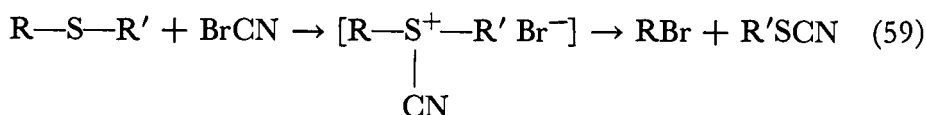


case of N-methylpiperidine, which is converted to 5-bromopentylmethylaniline through an N-cyano quaternary bromide (Eq. 58); the alkyl group

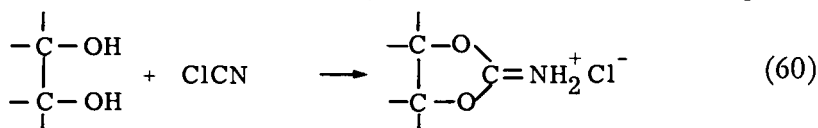


most susceptible to nucleophilic displacement at the α -carbon is presumably the one removed.

Sulfides are cleaved analogously; the alkyl group most susceptible to nucleophilic displacement appears as alkyl bromide ⁶² (Eq. 59).



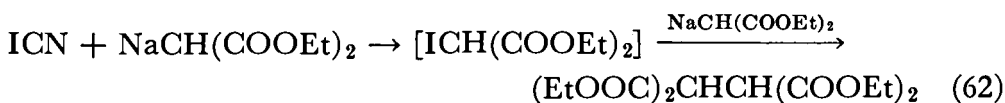
The reactions of cyanogen chloride with alkoxides or mercaptides to give cyanates or thiocyanates have been discussed in the foregoing section. With glycols, cyanogen chloride forms cyclic iminocarbonates ⁶³ (Eq. 60).



Carbanions generally attack the carbon of cyanogen halides, as in the case of cyanogen bromide and sodiomalonic ester, which yield cyanomalonate ^{64a} (Eq. 61). Cyanogen iodide, however, yields ethane-

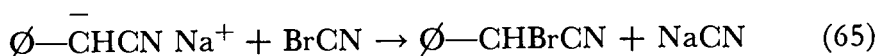
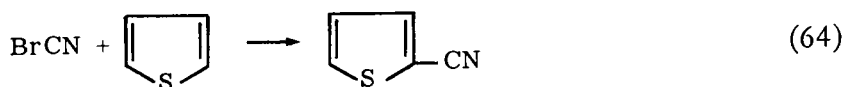
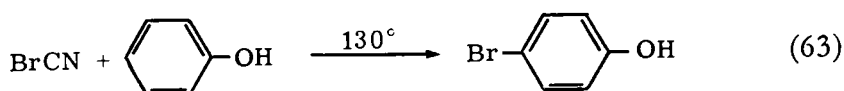


tetracarboxylic ester, an oxidation product, which may derive from iodination and reaction of the iodomalonic ester with more of the sodio compound (Eq. 62).

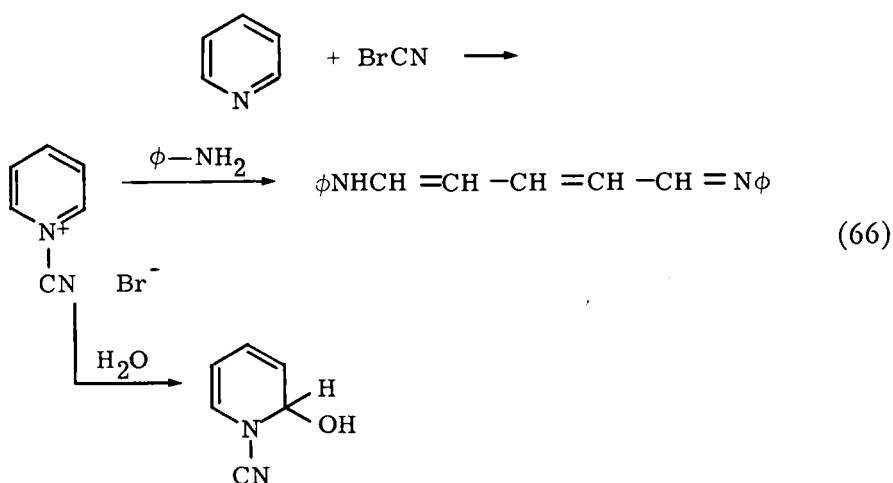


The different behavior of sodiomalonic ester toward BrCN and ICN illustrates a trend among the halogen cyanides to react increasingly as halogenating agents (sources of positive halogen) as the atomic weight increases (and the electronegativity of X decreases). Even BrCN will halogenate phenol, acetoacetic ester, and other active hydrogen compounds, ^{64b} for example, although toward thiophene it exhibits the opposite polarity and gives α -thenonitrile (Eqs. 63-65).

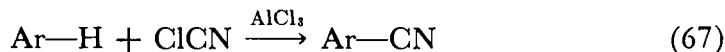
The reaction of cyanogen bromide with pyridines and quinolines takes place as with other tertiary amines, ^{65a} giving N-cyano pyridinium salts. These substances are useful as intermediates in pyridine and quinoline chemistry. Aniline reacts to give 5-anilinopentadienal anil, a



violet substance, making a useful qualitative test for pyridine ^{65b} (Eq. 66). Water gives a pseudo base (the 1-cyano-2-hydroxy-1,2-dihydro compound).



The cyanogen halides have not been found to add to olefinic double bonds ⁶⁶ in the manner of halogens, but they react substitutively with benzene rings under Friedel-Crafts conditions, giving benzonitriles in good yield ⁶⁷ (Eq. 67). Earlier reports of this reaction claimed that yields were



poor, owing to polymerization of the product, but it appears that the cyanogen halides that had been used must themselves have been largely polymerized to cyanuryl halides.

Cyanogen halides are easily reduced to halide and cyanide. Not only such inorganic reducing agents as hydriodic acid, hydrogen sulfide, and sulfurous acid will reduce them, but certain carbanions will as well, as mentioned earlier.

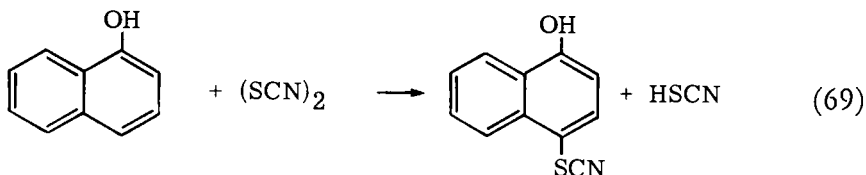
Cyanogen halides show the interesting ability to form complex ions reversibly with halide or cyanide ions, a property that is most pronounced with ICN and iodide. ⁶⁸ The formation of these complexes, XX'CN^- or X(CN)_2^- , is analogous to the formation of triiodide ion from iodine and iodide.

Thiocyanogen is usually generated *in situ* when it is wanted for reaction,

for it polymerizes at room temperature, and is broken up by water. It behaves very much like the halogens, and will add to the double bonds of olefins ^{44b, 69} (Eq. 68), and thiocyanate the more reactive aromatic



rings ⁷⁰ (Eq. 69). It will even attack metallic gold. It is apparently



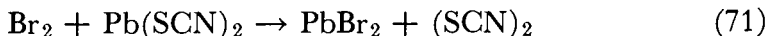
not basic, but it reacts with hydrochloric acid to give various five-membered heterocyclic rings that evidently arise in several steps involving addition of hydrogen chloride.⁷¹

Cyanogen chloride, bromide, and iodide are best prepared by the reaction of the free halogen with sodium or potassium cyanide (Eq. 70);



although even ICN is soluble in water, it will crystallize from strong solutions of potassium cyanide in which solid iodine has been dissolved. This reaction is quantitatively reversed in acid solution. In the case of ICN, it is necessary for good results that the quantities be controlled so as to avoid tying up the product as a complex ion.

Thiocyanogen can be prepared by oxidation of thiocyanic acid or its anion by various means, such as electrolysis of thiocyanate salts or the reaction of HSCN with lead tetraacetate, but the method of choice is the reaction of bromine with lead thiocyanate in dry ether at 0° (Eq. 71);



the resulting solution of thiocyanogen must, of course, be used promptly.

C. Cyanamides and Carbodiimides

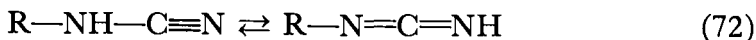
NOMENCLATURE Cyanamides are so called because they are just that, amides of cyanic acid. Substituted cyanamides are for the most part named by simply adding the name of the substituent, as "methylcyanamide," CH_3NHCN . A locant is not, of course, necessary, but sometimes "N-" is used, either for emphasis or for clarity in the case of two different substituents. Only with compounds distinctly inconvenient to name in this way is the cyanamide root name abandoned, as in "N-cyanocarbazole."

Carbodiimides bear that name because of their obvious relation to isoelectronic carbon dioxide. Substituents are named as prefixes, using N- and N'- as locants only when needed for clarity with two dissimilar substituents, as in "diethylcarbodiimide," $\text{C}_2\text{H}_5\text{N}=\text{C}=\text{NC}_2\text{H}_5$, and "N-benzyl-N'-methoxymethylcarbodiimide," $\text{C}_6\text{H}_5\text{CH}_2\text{N}=\text{C}=\text{NCH}_2\text{OCH}_3$.

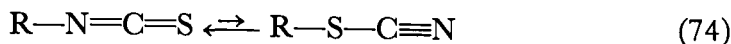
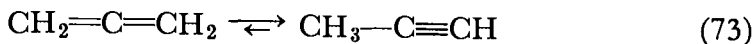
Carbodiimides are too reactive to occur in nature, although they may play a role as transient intermediates. The role of calcium cyanamide as a fertilizer and as the basic material for the industrial synthesis of a great variety of substances, from polymers to medicinals, is well known. The principal importance of carbodiimides is as reagents enabling the conversion of carboxylic and other acids to derivatives under mild conditions.

PROPERTIES Cyanamide itself forms large, glassy crystals, mp 40° , and is extremely soluble in both water and ether. The melting point is lowered by alkyl substitution, and dimethylcyanamide is a liquid, bp 160° , that freezes at -41° . It is completely miscible with water and all organic solvents except saturated hydrocarbons. Since there is no opportunity for hydrogen bonding, the solubility and low volatility must be attributed to a large dipole moment. Increasing the size of the alkyl groups has the expected effect of lowering the water solubility and increasing the hydrocarbon solubility; diethylcyanamide, fp -80.5° , bp 186° , is partially soluble in water (19% at 25°) and miscible with all types of organic solvents. Dialkylcarbodiimides are mostly liquids, of roughly similar volatility to the cyanamides, although they cannot be distilled at atmospheric pressure without decomposition. Dimethylcarbodiimide polymerizes too fast to have been obtained pure. The common reagent dicyclohexylcarbodiimide has bp $154\text{--}156^\circ/11\text{ mm.}$, mp *ca.* 20° .

Dialkylcyanamides show the usual $\text{C}\equiv\text{N}$ stretching frequency in the infrared near $2,250\text{ cm.}^{-1}$, whereas dialkyl carbodiimides absorb at $2100 \pm 5\text{ cm.}^{-1}$, the characteristic region for cumulative double bonds as found in allenes, ketenimines, and isocyanates. Cyanamide and its monoalkyl derivatives have spectral and many other characteristics resembling dialkylcyanamides rather than carbodiimides, from which facts it is inferred that the cyanamide structure is the far more stable and predominant one, in tautomeric equilibrium with small concentrations of carbodiimide (Eq. 72). Chemically, of course, a distinction cannot



be made for such rapidly tautomeric compounds, for they can react through either form. The triple-bond structure is evidently inherently more stable than the isomeric cumulative double-bond structure, as observed in the case of allene vs. acetylene, and it is only when other bonds of different energies must be altered that the cumulative system may become more stable, as in the case of thiocyanates vs. isothiocyanates (Eqs. 73, 74). The cyanamide ion, NCN^- , in crystalline salts is linear, and the two C—N distances are identical.

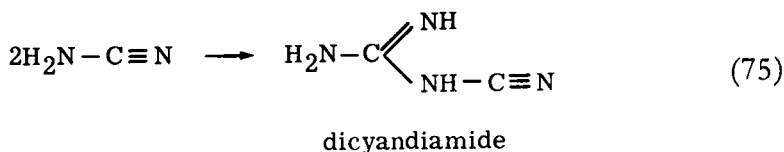


Both cyanamides and carbodiimides are very weakly basic (K_b ca. 10^{-15}), but will generally form salts or addition compounds with hydrogen chloride. The aliphatic members will dissolve in strong aqueous acids and can be recovered by prompt neutralization, but hydrolysis is rapid. Cyanamide is a dibasic acid, but only the first dissociation constant, 2.1×10^{-9} , is greater than that of water; consequently, salts such as the commercial CaNCN and Na_2NCN are completely hydrolyzed to the monoacid salts in water. Monosubstituted cyanamides are also acidic, of course; the acid strength may become quite great if the substituent is also strongly electron-withdrawing, as in the case of dicyanamide, NC—NH—CN .

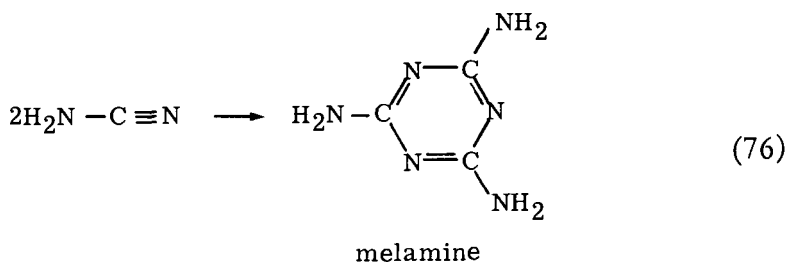
REACTIONS ⁷² Salt formation with metal ions occurs readily with cyanamide and its monosubstituted derivatives. Only the first hydrogen is replaced when alkali and alkaline earth hydroxides react, for the salts are soluble and the NCN^- ion is completely converted to NHCN^- by water. Heavy metal cyanamides, however, have solubilities similar to sulfides and acetylides, and some of them, such as Ag_2NCN , are so insoluble that they can easily be precipitated in water solution; cyanamide has even been proposed as a substitute for hydrogen sulfide as a precipitating agent in the traditional qualitative analytical scheme.

Both cyanamides and carbodiimides in general tend to polymerize on standing; the ease varies from very rapid with dimethylcarbodiimide to practical inertness with methyl-*tert*-butyl- and phenanthryl-phenyl carbodiimides. Polymerization may lead to dimers, trimers, or higher polymers, depending on structure and circumstances. In all cases, the polymerizations appear to be ionic in nature,⁷³ resulting in the formation of new bonds between a nucleophilic nitrogen and the electrophilic carbon.

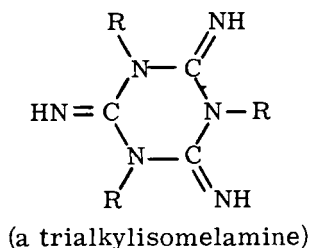
Cyanamide itself slowly dimerizes on standing to form "dicyandiamide," cyanoguanidine (Eq. 75). It is thus useless to attempt to store



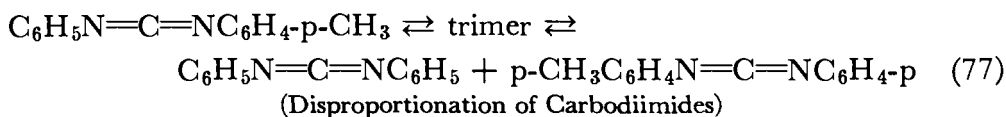
cyanamide for months on the shelf, even though it can be bought commercially. Strong heating causes polymerization of a different type, analogous to that of cyanic acid, resulting in the triamide of cyanuric acid, called melamine (2,4,6-triamino-*sym*-triazine) (Eq. 76). Monosubstituted cyanamides polymerize similarly when warmed; the products are trialkylisomelamines. Phenylcyanamide polymerizes on standing to form an apparent heptamer which has been shown to be an addi-



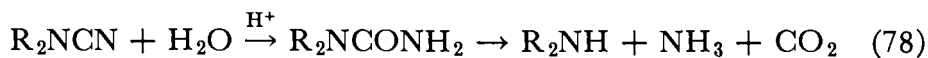
tion compound of two moles of triphenylisomelamine and one mole of phenylcyanamide.⁷⁴



The polymers of carbodiimides have been only incompletely investigated, but it appears that the trimers that are often formed are also *sym*-triazines, derived from isomelamine with one substituent on each nitrogen. Carbodiimides with different substituents disproportionate on heating, apparently through formation and redissociation of such trimers⁷⁵ (Eq. 77).

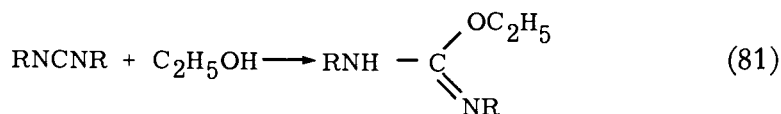
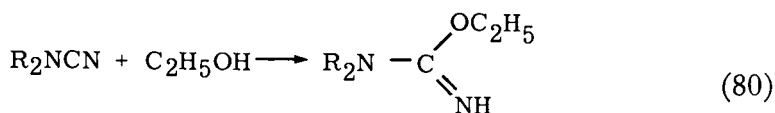


The most well-developed behavior of both cyanamides and carbodiimides is the addition of nucleophiles at the carbon atom. Thus the first step of hydrolysis, catalyzed by acid, is the formation of a urea; hydrolysis of the ureas to amines and carbon dioxide takes place subsequently, but is slower (Eqs. 78 and 79). The addition of hydrogen

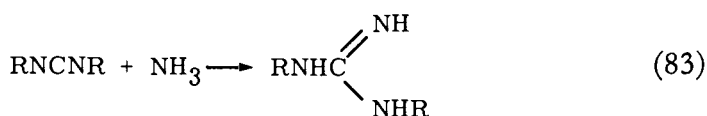
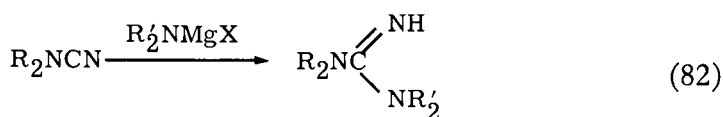


sulfide gives thioureas analogously, and has preparative value for unsymmetrically disubstituted compounds.⁷⁶ Alcohols and mercaptans add analogously, but owing to the immobility of the alkyl groups, the products are O-alkyl isoureas (or their sulfur analogues)⁷⁷ (Eqs. 80, 81).

Ammonia and primary and secondary amines add readily in the same way as water and alcohols; the products are guanidines, for which this reaction is an important synthetic method.⁷⁸ These additions are



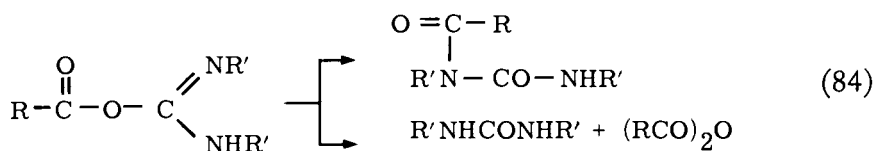
markedly accelerated by use of an ammonium salt or a sodium or magnesium salt of the amine (Eqs. 82, 83).



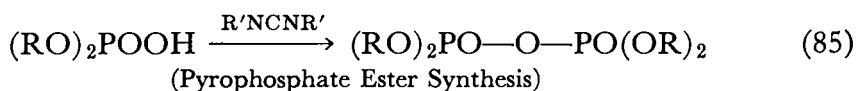
The spontaneous reaction of carboxylic acids with carbodiimides pro-

duces O-acylisoureas, $RCOO - \overset{\overset{NR'}{\mid}}{\underset{\underset{NHR}{\mid}}{C}}$; these are reactive and unstable

compounds. If other reactions do not intervene, they react further by two competing paths, to produce either an N-acylurea (rearrangement), or a urea and the anhydride of the acid ⁷⁹ (Eq. 84). The first reaction



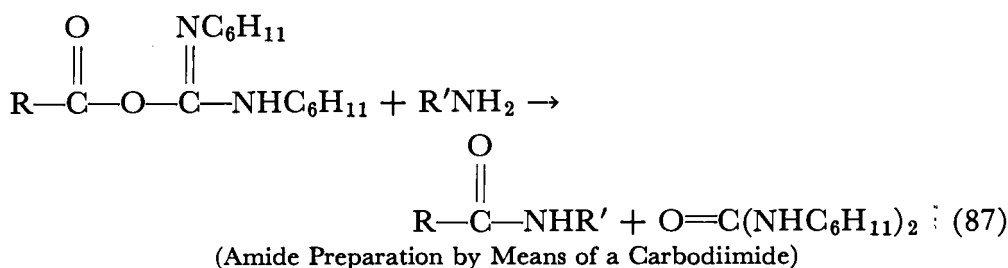
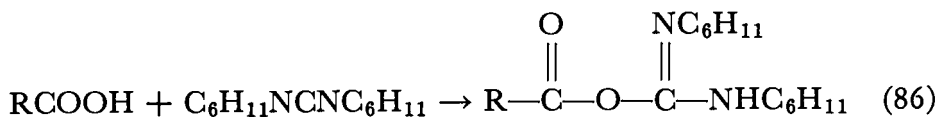
predominates with diarylcarbodiimides, and has been proposed as a general method for preparing crystalline derivatives of acids. The anhydride-forming reaction occurs not only with carboxylic acids, but also with sulfonic and phosphoric acids ⁸⁰ (Eq. 85), and is of great impor-



tance in the synthesis of nucleotides.

The greatest importance of the reaction between carboxylic acids and carbodiimides arises from the acylating ability of the O-acylisoureas

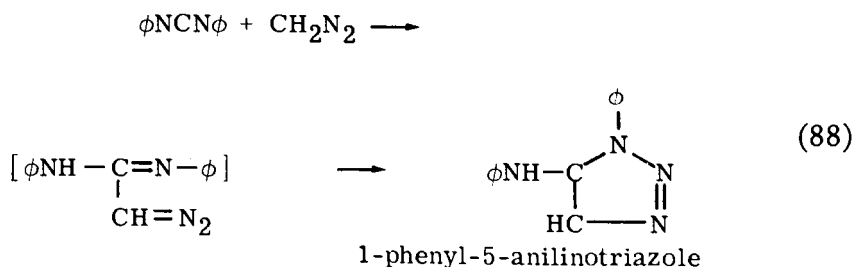
first formed, which are mixed carboxylic-carbamimidic anhydrides. The carbonyl group in these is the most reactive site, and if a suitable nucleophile, such as primary or secondary amine, sometimes even a phenol, is present, it can be acylated under very mild conditions (Eqs. 86-87).



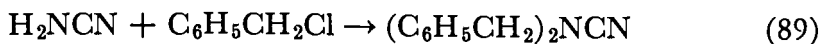
The method is exceptionally useful in building up the amide links of peptide chains. Dicyclohexylcarbodiimide is the reagent commonly used.

Potential carbanions react with cyanamides and carbodiimides in the manner of other nucleophiles, adding to the carbon.⁸¹ When there are no acidic hydrogens, Grignard reagents can be used; the products are disubstituted amidines.

Diazomethane and hydrogen azide apparently also add to carbodiimides as nucleophiles, but the resulting guanyl compounds react further to close a five-membered ring⁸² (Eq. 88).

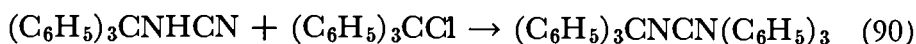


Carbodiimides are apparently too weakly nucleophilic to react with alkylating agents, but cyanamide and its monoalkyl derivatives react either as such, or in the form of their salts, with alkyl halides. It is hard to stop the reaction at the monoalkyl stage, but the reaction is a preparatively useful one for disubstituted cyanamides⁸³ (Eq. 89). Only in the

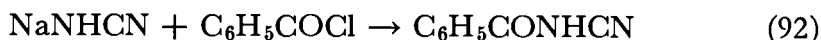
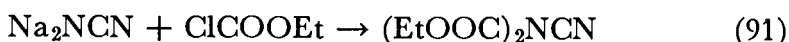


presence of pronounced steric hindrance, as in the reaction of triphenylmethylcyanamide with triphenylmethyl chloride, does the second sub-

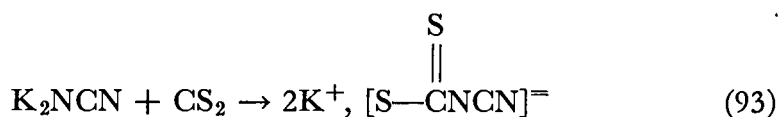
stituent add to the unsubstituted nitrogen to produce a carbodiimide ⁸⁴ (Eq. 90).



Acylation of cyanamide and its monosubstituted derivatives can be accomplished through their salts by reaction with acid anhydrides or chlorides ⁸⁵ (Eqs. 91, 92). Both mono- and di-acyl compounds can be



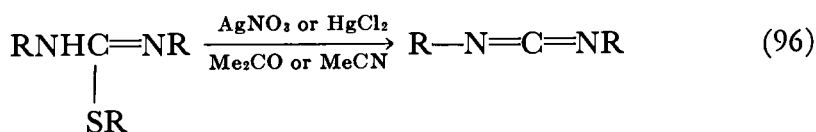
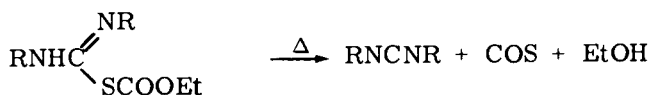
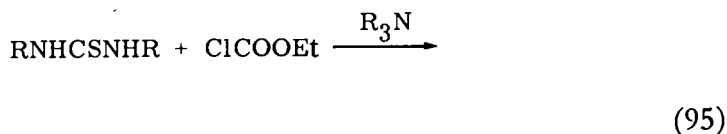
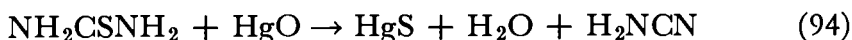
obtained. Carbon dioxide and disulfide give cyanocarbamate derivatives ⁸⁶ (Eq. 93).



Little attention has been paid to reduction of carbodiimides or cyanamides, but a case of hydrogenation of a disubstituted cyanamide to a secondary amine and methylamine has been reported.⁸⁷

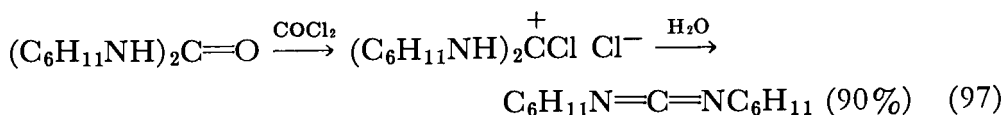
PREPARATION The most general method for preparing both cyanamides and carbodiimides is removal of the elements of hydrogen sulfide from thioureas (Eq. 94). Compounds of all degrees of substitution, alkyl or aryl, can be prepared in this way. Mercuric oxide is the commonest reagent,⁸⁸ but the result has been accomplished by chlorination ⁸⁹ (a

guanyl chloride hydrochloride, $(\text{RNH})_2\overset{+}{\text{C}}\text{Cl} \text{Cl}^-$, is the intermediate), and by heating S-acyl or S-alkyl derivatives, alone ⁹⁰ or with silver nitrate or mercuric chloride ^{51a} (Eqs. 95, 96), a reaction resembling the modified Kaluza



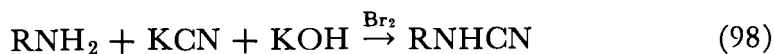
reaction for preparing isothiocyanates. In an analogous reaction, ureas have been dehydrated with toluenesulfonyl chloride and pyridine or with

phosgene ⁹¹ (Eq. 97), a reaction not unlike the dehydration of amides to



nitriles. The removal of ammonia from guanidine, which accomplishes the same result, occurs in 80–90% yield with nitrous acid.⁹²

A method of wide and satisfactory application for cyanamides is the reaction of cyanogen halides with amines.^{60, 61, 87} The isolation of the objectionable cyanogen halides has been avoided by treating a mixture of amine and potassium cyanide with bromine, generating cyanogen bromide *in situ* ⁹³ (Eqs. 98, 99). The complementary reaction, that of



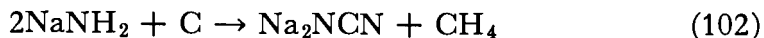
chloramines with potassium cyanide, has also been accomplished ⁹⁴ (Eq. 100).



Cyanamide itself is available cheaply and in enormous quantities commercially, as its calcium salt, prepared from calcium carbide and nitrogen in an electric furnace (Eq. 101). Sodium cyanamide can be

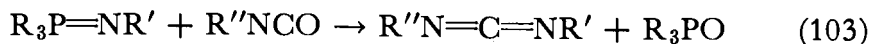


prepared by heating sodamide with carbon at 400° (Eq. 102). It is



possible to isolate free cyanamide from its salts, but the process is troublesome owing to the quantity of inorganic salts that must be separated, the high water solubility of cyanamide, and its sensitivity to hydrolysis and polymerization.

There are a number of other, interesting but so far less important, synthetic methods for cyanamides and carbodiimides, such as the Tiemann reaction of amidoximes,⁹⁵ the decomposition of various heterocyclic systems (tetrazoles,⁷⁵ thiatriazoles,⁹⁶ oxadiazetidines⁹⁷), and the reaction of phosphine imines with isocyanates or carbon dioxide ^{36c, 98} (Eq. 103).



Whereas the last reaction converts isocyanates to unsymmetrical carbodiimides, the symmetrical variety can be obtained from the same starting

material by disproportionation induced by phosphine oxides,^{36a,b} often in very high yields (Eq. 104).



COMPOUNDS WITH TRICOÖRDINATE CARBON

A. Carbamic and Carbonimidic Acid Derivatives (Urethans, etc.)

NOMENCLATURE The name "carbamic acid" for NH_2COOH is formed in the systematic way for naming the half amide of symmetrical dibasic acids, by use of the infix "-am-," with elision of the penultimate syllable. (Other common examples are oxamic acid, NH_2COCOOH , and succinamic acid, $\text{NH}_2\text{COCH}_2\text{CH}_2\text{COOH}$.) The esters and salts are thus called "carbamates," and the acyl radical $\text{NH}_2\text{CO}-$ is called "carbamyl" or "carbamoyl." N-Phenylcarbamic acid is the half anilide of carbonic acid, and is accordingly called "carbanilic acid," and so listed in *Chemical Abstracts*.

Ethyl carbamate, $\text{NH}_2\text{COOC}_2\text{H}_5$, was identified early in the history of organic chemistry, before the advent of systematic nomenclature, and was given the name "urethane" because of its resemblance to urea and the presence of an ethyl group. The name was adopted as a convenient root name, allowing substituted compounds to be named in such a manner as "N-methylurethane," $\text{CH}_3\text{NHCOOC}_2\text{H}_5$. The term has even been used to designate the whole class of carbamate esters. By international agreement, the word was officially changed to "urethan," in order to reserve the "-ane" ending strictly for saturated hydrocarbons. Carbamate esters other than ethyl are sometimes given names based on the urethan root; in such cases one must be particularly careful to avoid ambiguity as to the location of the alkyl group(s). A name such as "*n*-propyl N-methylurethan" is understandable for $\text{CH}_3\text{NHCOOCH}_2\text{CH}_2\text{CH}_3$, but there is really no justification for not using the systematic name, "propyl N-methylcarbamate."

Both monothio and dithio analogues of carbamates are known. Two isomeric alkyl monothiocarbamates are obviously possible; they are distinguished by the prefixes "thion-" for the structure bearing a thiocarbonyl group, and "thiol-" for the isomer, as in $\text{NH}_2\text{COC}_2\text{H}_5$, "ethyl



thioncarbamate," and $\text{NH}_2\text{CSC}_2\text{H}_5$, "ethyl thiolcarbamate." Deriva-



tives of the type $(R_2NCS)_2S$ and $(R_2NCS)_2S_2$ have the special names "thiuram sulfide" and "disulfide." The urethan structure has great potentiality for physiological activity, and even urethan itself has been used as a hypnotic drug and as a growth inhibitor. *N*-*sec*-Amylurethan is the commercial hypnotic "hedonal." Thiuram derivatives are of importance as vulcanization accelerators and as pesticides.

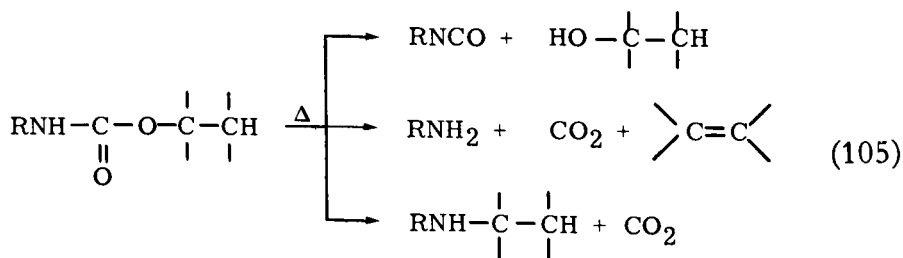
PROPERTIES ⁹⁹ Urethan itself is a well-crystallized but low-melting substance (mp 50° , bp 184°), freely soluble in water, ether, and all common organic solvents. Substitution of the hydrogens by alkyl groups has the effect to be expected when the opportunity for hydrogen bonding is reduced: the melting point drops, and the boiling point is either lowered (*N*-methylurethan, bp 170°), or not increased as much as would result from simple increase in molecular weight. Carboethoxyurethan, more properly called ethyl iminodicarboxylate, $HN(COOC_2H_5)_2$, mp 50° , bp $132\text{--}133^\circ/12\text{ mm.}$, and ethyl nitrilotricarboxylate, $N(COOC_2H_5)_3$, bp $147^\circ/12\text{ mm.}$, are also known.

Carbamoyl chloride, NH_2COCl , mp 50° , bp $61\text{--}62^\circ$, and its monoalkyl derivatives are much more volatile than one might suppose, owing to the fact that they dissociate reversibly on warming into HCl and $HNCO$ (or $RNCO$). The dialkylcarbamoyl chlorides, such as $(CH_3)_2NCOCl$, bp 167° , are much less volatile.

Although free carbamic acids are too unstable for isolation, dithiocarbamic acid has been obtained as colorless needles that decompose quickly in water.

Urethan is neutral in water solution, like other carboxamides. It is acidic enough to form salts in the absence of water, and one can infer that it is somewhat more acidic than ordinary carboxamides from the fact that carbonic acid (actual H_2CO_3 , as opposed to carbon dioxide) is stronger than such fatty acids as acetic and benzoic.

REACTIONS Urethans in general are quite stable compounds that can be stored indefinitely. They are decomposed by heating to moderate temperatures, however, and then give products arising from three distinct paths (Eq. 105) ^{99b, 100}: elimination of an alcohol (or phenol) with forma-



(thermal decomposition of urethans)

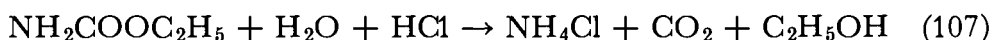
tion of an isocyanate; elimination of carbamic acid (as amine and carbon

dioxide) with the formation of an olefin; and decarboxylation to form an amine and carbon dioxide. The temperatures required may be as low as 50° with *tert*-alkyl carbamates, but are more often in the neighborhood of 200°. The choice of paths depends very much on structure, and phenyl carbamates, for example, decompose near 150° almost exclusively to phenol and isocyanate.

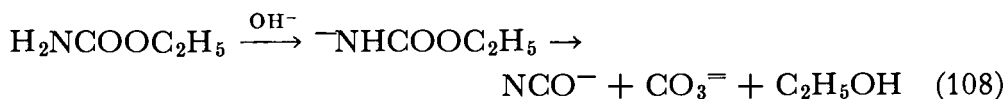
Urethan itself will react with metallic sodium to form a salt (Eq. 106),



and there is reason to believe that the anion can even be produced by strong alkali. The normal hydrolysis products to be expected of urethan as an amide and an ester are ammonia, carbon dioxide, and alcohol, and these are indeed formed when aqueous acid or base is used (Eq. 107).



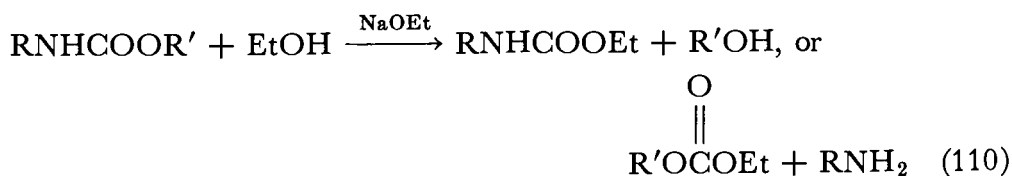
However, alcoholic potassium hydroxide converts urethan to ethanol and potassium cyanate.¹⁰¹ The latter product could not reasonably arise from addition of hydroxide ion to the carbonyl group, but could arise simply by fission of the anion (Eq. 108).



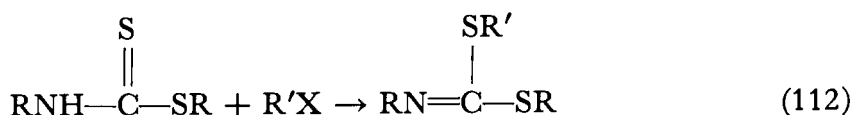
The carbonyl group of urethans, like all carbonyl groups, is susceptible to attack by nucleophiles, but as would be expected of an amide, the reactivity is rather sluggish. It is owing to this low electrophilic reactivity of the carbonyl group that the alkali-catalyzed fission just mentioned can occur. Urethan will nevertheless react with ammonia or amines on heating, forming ureas^{102a, b} (Eq. 109), whereas sodium alkoxides bring



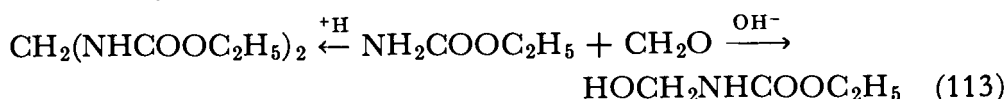
about alcoholysis,^{102c} either as transesterification, or to form a carbonate ester and amine (Eq. 110).



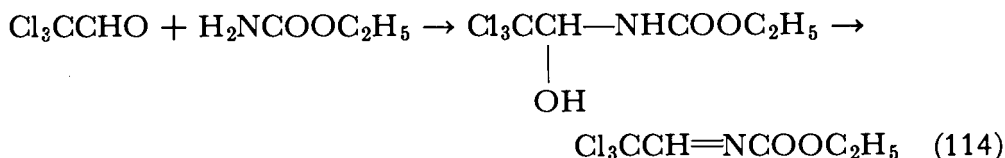
Urethan is also a poor nucleophile, and does not readily react with alkylating agents except as the sodium salt. By that route, however, it is readily alkylated by alkyl halides¹⁰³; dithiourethans, however, react directly with alkylating agents to form iminodithiocarbonate esters¹⁰⁴ (Eqs. 111, 112).



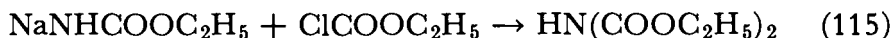
Urethan reacts as a weak nucleophile toward aldehydes, in the manner of other amides, and gives addition products whose structure depends on the nature of the reaction medium. In the presence of base, formaldehyde, for example, gives N-methylolurethan, but in the presence of acid, methylenediurethan is produced ¹⁰⁵ (Eq. 113). Chloral, however,



gives a carbinolamine derivative that can be dehydrated to the aldimine ^{105b} (Eq. 114).

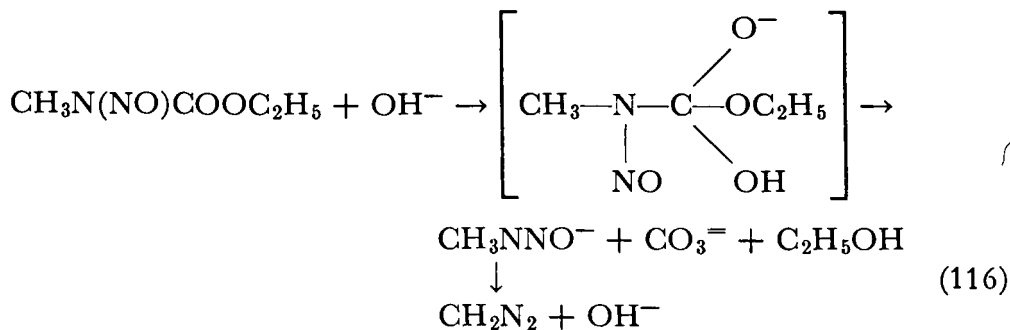


Acylation of urethans is possible when the amido group is not completely alkylated. With urethan itself, ¹⁰⁶ acetic anhydride or acetyl chloride gives N-acetylurethan; the sodium salt can also be used (Eq. 115).



Nitrosation can be accomplished with "nitrous fumes" (principally $\text{N}_2\text{O}_3 \rightleftharpoons \text{NO} + \text{NO}_2$), leading to a group of irritating substances, the N-alkyl-N-nitrosourethans, at one time of much use to the organic chemist as sources of diazoalkanes (see Chapters 10, 16).

N-alkyl-N-nitrosourethans react with strong alkali to produce ethanol, carbonate, and salts of nitrosamines (an alkyl diazotates).¹⁰⁷ The last are very unstable, and can only be isolated under special conditions; they break up under the usual conditions to give a diazoalkane, which is distilled over with ether (Eq. 116).



(Formation of Diazomethane from N-Methyl-N-Nitrosourethan)

Nitration can be accomplished in the presence of concentrated sulfuric acid, leading in the case of urethan itself to nitrosourethan, $\text{O}_2\text{NNH-COOC}_2\text{H}_5$, a strongly acidic substance. It is interesting that careful reduction of this compound by zinc leads to N-nitrosourethan, and is the best preparative method for it.¹⁰⁸ Urethans are inert toward cyanic acid,¹⁰⁹ but form allophanates when dry hydrogen chloride is present. Hypochlorous acid or aqueous chlorine converts urethans to N-chloro derivatives.¹¹⁰

Urethans are not ordinarily susceptible to oxidation, although drastic conditions will undoubtedly attack the alkyl groups. Urethans are also resistant to reduction, like amides and esters in general, but lithium aluminum hydride can convert the carboalkoxy group into a methyl group, producing an amine¹¹¹ (Eq. 117).



Carbamoyl chlorides are reactive acylating agents like other acyl chlorides, and react in the usual manner with alcohols to produce esters (urethans) and with amines to produce amides (ureas). The easy dissociation of monoalkylcarbamyl chlorides has already been mentioned; it is an intermediate step in the preparation of isocyanates by the reaction of primary amines with phosgene (see Part A and Chapter 2).

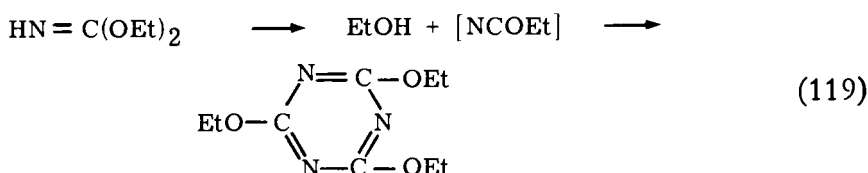
Carbamic acid itself has never been isolated. Although salts are easily prepared, treatment of them with a strong acid results in spontaneous fission to an amine and carbon dioxide. Similar remarks apply to thiocarbamic acid, but dithiocarbamic acid, NH_2CSSH , has been isolated. It decomposes rapidly in solution, giving thiocyanic acid and ammonium thiocyanate. Carbamate salts are formed when ammonia or primary or secondary amines react with carbon dioxide (or carbon oxysulfide, COS , or carbon disulfide)¹¹² (Eq. 118). The crystal-



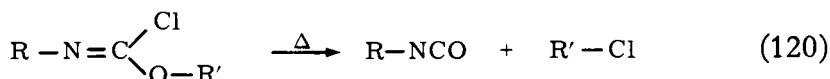
line rime that often forms about the mouths of bottles containing amines is a carbamate salt. Ammonium carbamate is an article of commerce, and is an intermediate in the production of urea from ammonia and carbon dioxide.

IMIDOCARBONATES Although carbamates are derivatives of the amide tautomer, $\text{NH}_2\text{—CO—OH}$, of carbamic acid, it is also possible to have derivatives of the imidic acid structure, $\text{HN}=\text{C}(\text{OH})_2$, imidocarbonic (carbonimidic) acid. They are relatively little known, however. Ethyl imidocarbonate,¹¹³ $\text{HN}=\text{C}(\text{OC}_2\text{H}_5)_2$, is an oil, bp $62^\circ/36$ mm. It loses ethanol on standing and deposits triethyl cyanurate, undoubtedly derived

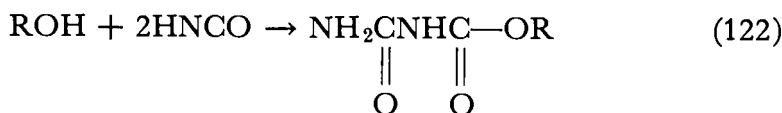
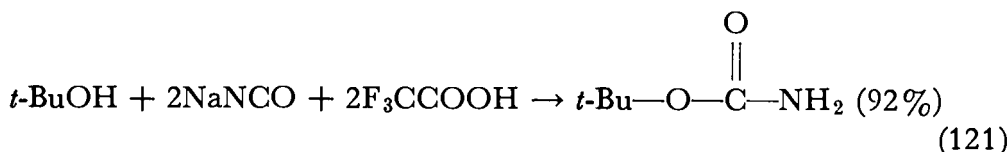
from ethyl cyanate (Eq. 119). Iminocarbonates readily undergo the



Chapman rearrangement (Chapter 4) when heated, producing N-aryl urethans quantitatively.¹¹⁴ The half-ester half-chlorides (alkoxyformimidoyl chlorides) are known; they readily eliminate alkyl chloride to form isocyanates (Eq. 120).

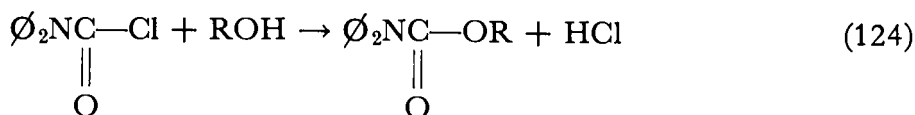
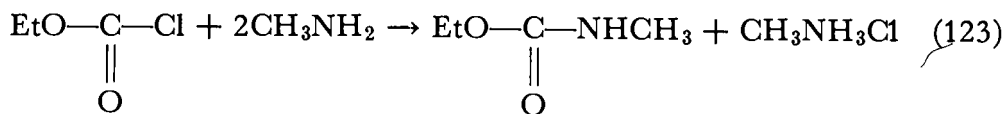


PREPARATION The commonest general reaction for preparing urethans is that of isocyanates with alcohols (Eq. 14). It is usually spontaneous and essentially quantitative, although slower with phenols, and is familiar as a general method for making derivatives of alcohols for characterization.^{23, 24, 115} Urethans are often prepared by this reaction without actually isolating the isocyanate; instead, the isocyanate is prepared *in situ* by the Curtius rearrangement of an acyl azide.⁴⁷ Cyanic acid itself can be used to produce unsubstituted urethans,^{116a} but this reagent may also give rise to allophanates, the esters of carbamylcarbamic acid (Eqs. 121, 122). Allophanates are well crystallized substances, and

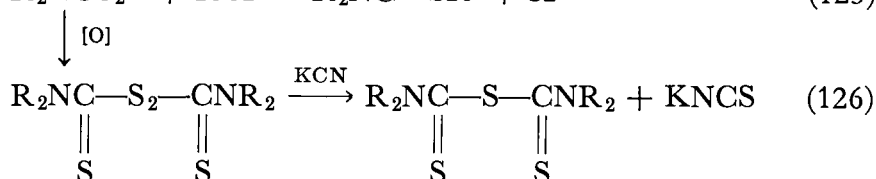
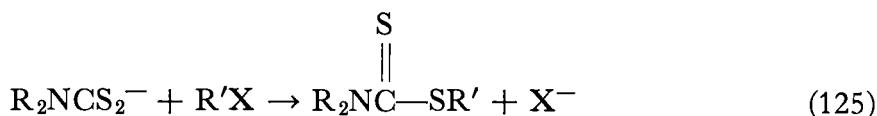


have also been used as derivatives for the identification of alcohols.^{116b,c}

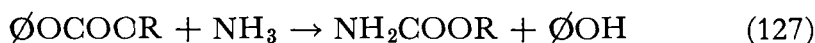
Since urethans are both esters and amides, they can be prepared by the standard methods for such functions, namely, the reaction of acid chlorides with alcohols or amines¹¹⁷ (Eqs. 123, 124).



Dithiourethans are usually prepared by alkylation of dithiocarbamate salts ^{99b} (Eq. 125). Thiocarbamyl disulfides (thiuram disulfides) are also prepared from thiocarbamate salts, various oxidizing agents, such as ferricyanide, hydrogen peroxide, or iodine, being suitable reagents.^{99b} The monosulfides are best prepared from the disulfides, usually by partial desulfurization with potassium cyanide (Eq. 126).



Urethans can also be prepared by the aminolysis of carbonate esters, particularly alkyl phenyl carbonates ^{117d} (Eq. 127).



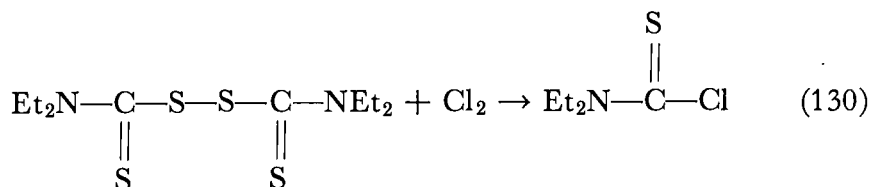
Carbamyl chlorides are prepared by the reaction of amines with phosgene (carbonyl chloride) (Eq. 128), or by the addition of hydrogen



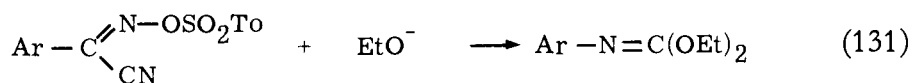
chloride to isocyanates ^{51c, 118} (Eq. 129). Thiocarbamoyl chlorides are



prepared by the chlorinolysis of thiuram disulfides ^{118d} (Eq. 130). Imino-



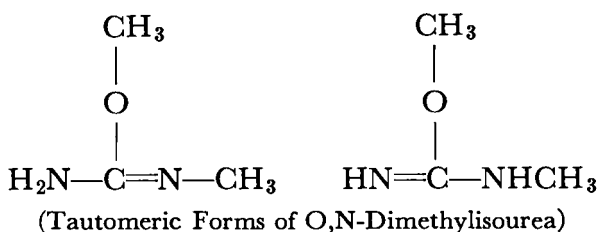
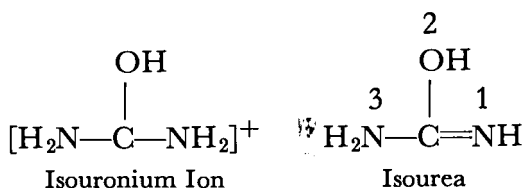
carbonates have been prepared by the treatment of α -oximino nitriles with sodium ethoxide ¹¹⁹ (Eq. 131), by aminolysis of ethyl orthocar-



bonate,^{114b} and by reaction of alkoxides with carbonimidoyl chlorides, $\text{RN}=\text{CCl}_2$, or alkoxyformimidoyl chlorides, $\text{RN}=\text{CClOR}$. Carbonimidoyl chlorides are prepared by treating isothiocyanates ^{40b,c} with chlorine, or by the addition of halogen to isocyanides (see Chapter 5).

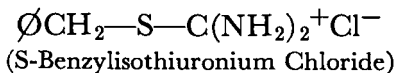
B. Urea, Isourea, and Derivatives

NOMENCLATURE Urea, H_2NCONH_2 , is the amide of carbonic acid, and is therefore sometimes called "carbamide." The position of substituents is usually indicated by the use of N and N', but numbering is favored by some indexers, the two nitrogen atoms being designated 1 and 3. The tautomeric imidic acid structure, which has not been separately isolated, is called "isourea," or occasionally "pseudourea." Substituents are indicated either by O, N, and N', or by numbers. It is



rarely necessary to distinguish which nitrogen is doubly bonded and which singly, for tautomeric interconversion is so easy that isomeric N-mono-substituted isoureas, as shown, cannot be separately isolated. In salts of isourea, the cation is named "isouronium."

Thiourea and isothiurea and derivatives are designated by the obvious inclusion of the prefix "thio"; in naming the cations derived from isothiurea, chemists customarily elide a vowel, giving rise to the form "isothiuronium."



PROPERTIES Urea¹²⁰ itself is a colorless, well-crystallized solid, mp 132.7°. It was first discovered, by isolation from urine, by F. M. Rouelle in 1773, and has the distinction of being the first organic compound to be synthesized from inorganic materials, by F. Wöhler, 52 years later.¹²¹ In extreme contrast to the oxygen analogue, carbonic acid, urea is not only isolable, but can be stored indefinitely at room temperature. It is extremely soluble in water, forming a 50% solution at room temperature and becoming completely miscible in boiling water; it is nearly insoluble in ether and hydrocarbons, however. It is a very polar substance, showing strong hydrogen bonding.

An enormous number of substituted ureas are known, such as methylurea, mp 102°, N,N'-dimethylurea, mp 106°, and N,N-dimethylurea,

mp 182°. Complete substitution of the hydrogens lowers the melting point drastically, and tetraethylurea is an oil with a peppermint odor, bp 210–215°.

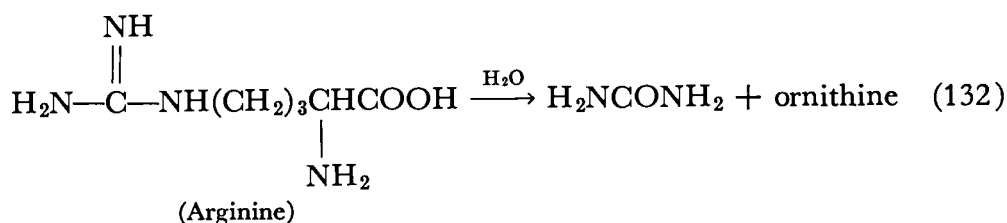
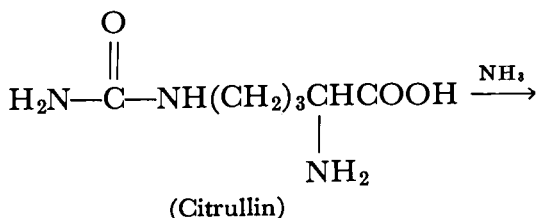
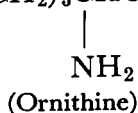
The structure of urea was controversial for a long time, for although there was no question that it was the amide of carbonic acid, the ordinary structure did not seem to explain the properties satisfactorily. Much of the argument was resolved when the structure of crystalline urea was determined by X-ray diffraction¹²²; the two nitrogen atoms were found to be completely equivalent, but the C—N distance, 1.37 Å, noticeably shorter than the C—N distance in saturated compounds, showed that there was strong electronic interaction. In polar solvents, a tautomeric equilibrium is set up, and a few per cent of the isourea form is present.¹²³

Urea is both a very weak base and a very weak acid. The basic dissociation constant¹²⁴ (for the reaction $\text{H}_2\text{NCONH}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{NCONH}_3^+\text{OH}^-$) is about 10^{-14} , similar to that of water itself and slightly weaker than carboxamides. The acidity is too weak to be detected in water solution, although urea forms salts under some conditions.

Isoureas are not as well known. They are much more strongly basic than ureas, and resemble amidines more than amides. O-Methylisourea, $\text{CH}_3\text{OC}(=\text{NH})\text{NH}_2$, mp 45°, bp 82°/9 mm., has a basic dissociation constant^{125a} of 6.4×10^{-5} , distinctly greater than that of ammonia. The properties of many other examples have been recorded.^{125b}

Thiourea, mp 182°, has properties very similar to those of urea, but it is a weaker base by about one power of 10, and shows the general phenomenon that the melting points of the sulfur analogues are usually higher than those of the parent compounds. It is much less soluble in water than is urea, and is slightly soluble in ether. Tetramethylthiourea, $(\text{CH}_3)_2\text{NCSN}(\text{CH}_3)_2$, has mp 78°, bp 245°, and is soluble in both water and ether. Thiourea forms a sodium salt with sodamide in liquid ammonia, and also forms addition compounds with ammonia. Many S-alkyl isothioureas are known, but in most cases only as their salts, the free bases being unstable and difficult to isolate. S-Methylisothiourea melts with decomposition at 79°, is soluble in water and in ether, and has a basic dissociation constant of about 10^{-4} ($\text{pK}_a = 9.83$).¹²⁶

In addition to its great historical importance in organic chemistry, urea has great physiological importance, for it is the substance by which the human organism gets rid of unwanted nitrogen; the average man excretes an ounce a day. The mechanism by which ammonia is scavenged as urea was elucidated in 1932 by H. Krebs and H. Henseleit¹²⁷: The diamino acid ornithine reacts with ammonia and carbon dioxide to form a ureido acid, citrullin. This reacts with more ammonia to form a guanidino acid, arginine, which is subsequently hydrolyzed back to ornithine and a molecule of urea (Eq. 132).



Urea also has great commercial significance, since it is used as a fertilizer, as a component of urea-formaldehyde resins, and as a starting material in the synthesis of many drugs of the barbiturate type.

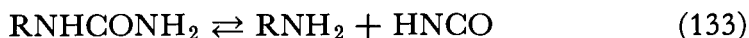
REACTIONS *Salts* Although ureas are scarcely more basic than water, they can still form salts with strong acids. The salts are, of course, almost completely hydrolyzed in dilute solution. Aryl ureas usually show basic properties only toward concentrated sulfuric or phosphoric acids. Urea nitrate has a rather low solubility in nitric acid, and has even been used for the gravimetric estimation of urea. Thiourea also forms salts with strong acids. O-Alkylisoureas and S-alkylisothioureas, being much stronger bases, dissolve readily even in dilute acid to form salts, and the majority of them are only known in salt form.

Inclusion compounds Urea has the remarkable property of forming "inclusion compounds" with straight-chain aliphatic compounds including hydrocarbons, when the chain has seven or more atoms in it.¹⁰³ The included compounds are not bound to urea by chemical bonds, but fit into the crystal lattice. It is the requirements of the fit that make urea so selective for unbranched compounds. The phenomenon is used industrially to separate straight-chain compounds from the mixtures occurring in petroleum, in order, for example, to use them for preparing synthetic detergents that are biodegradable and thus capable of being destroyed in sewage disposal plants. Urea also forms addition compounds with salts, such as sodium chloride. With hydrogen peroxide urea gives a product useful as an easily handled and stored source of peroxide, marketed under various trade names, such as "Hyperol," "Ortizone," and "Perhydrite."

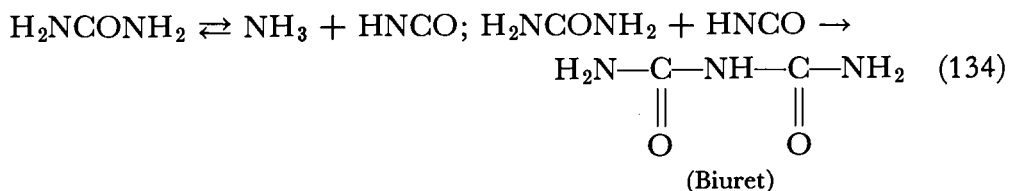
The acidity of ureas is so low that the formation of metal ureides in

the presence of water ordinarily occurs only with those metal ions that form very insoluble or slightly ionized salts, such as disilver ureide and mercuric ureide, formed by the reaction with silver oxide or mercuric acetate, respectively. Alkali metal amides and hydrides react with urea to form such salts as KNHCONH_2 or $\text{K}_2(\text{NHCONH})$, depending on the proportions. Thiourea forms complexes with some heavy metal ions, and the bright yellow color formed with bismuth salts has been used as a qualitative test for that metal. Silver, mercuric, and lead compounds remove hydrogen sulfide, however, forming insoluble metal sulfides and a cyanamide or carbodiimide; the use of this reaction for preparative purposes has already been mentioned (Part 2). Aryl thioureas are sometimes acidic enough to dissolve in aqueous alkali, but are reprecipitated by carbon dioxide.

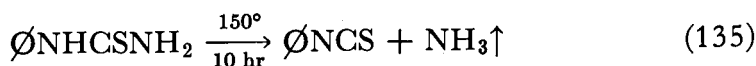
Heat Most ureas are decomposed by heating,¹²⁹ usually just above the melting point, and cannot therefore be distilled; fully substituted ureas are more stable, however. The common path of decomposition is cleavage into an amine and cyanic acid, the reverse of one of the general preparative methods for ureas (Eq. 133). This dissociation even occurs



in hot-water solutions, and about 5% of cyanic acid can be detected in hot aqueous urea solutions. Since cyanic acid is unstable and reacts further in other ways, these dissociations slowly go to completion. The common fate of cyanic acid is condensation to cyanuric acid, but when the heating is mild, it may react with unchanged urea, producing biurets (Eq. 134). This can be used as a sensitive qualitative test for urea,¹³⁰

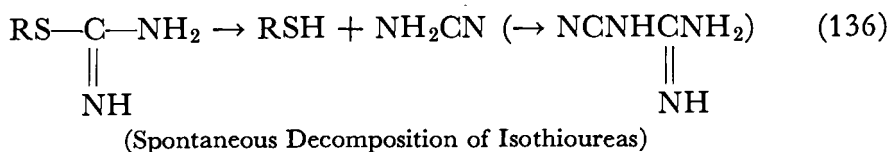


for biuret forms an intense purple color with cupric salts. Disproportionation can also occur when substituted ureas or thioureas are heated strongly. Phenylurea, for example, is converted to N,N'-diphenylurea and urea at 160°, and when N,N'-diphenylurea is heated above its melting point (235°), it is slowly converted into triphenylguanidine (and other products).¹³¹ Thioureas undergo analogous reactions on heating⁵⁶ (Eq. 135), except that products of the biuret type are not important, a conse-

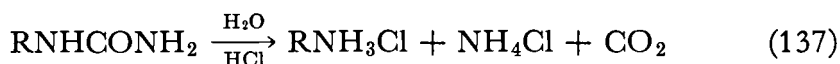


quence of the relative inertness of isothiocyanates toward weakly basic amino groups.

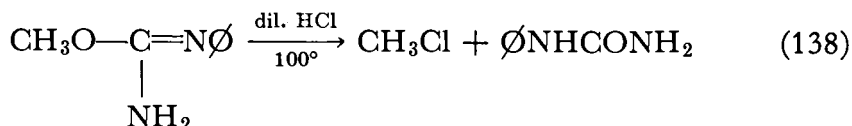
The isourea structure is quite stable as the cation, but the free bases are quite sensitive substances. S-Alkylisothioureas decompose even on standing, or heating, giving mercaptans and cyanamides or carbodiimides ^{90b} (Eq. 136).



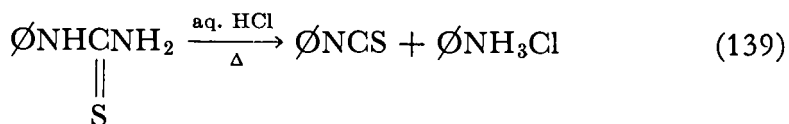
Hydrolysis Since all ureas are amides of carbonic acids, they can be hydrolyzed ultimately to carbon dioxide and ammonia or amines (Eq. 137). Such hydrolysis is not easy, especially with aryl ureas, and pro-



longed heating under pressure with strong mineral acid or with alkali may be required in extreme cases. Phenylurea, for example, remains largely unaltered by boiling to dryness with concentrated hydrochloric acid. Hydrolysis of urea can also be accomplished with the enzyme urease, found in soy beans (and elsewhere), or by bacterial action. O-Methyl isoureas are demethylated by hydrochloric acid before hydrolysis takes place (Eq. 138).¹³²



Thioureas are often very difficult to hydrolyze, and, indeed, the first step in the acid-catalyzed process is dissociation into amine and isothiocyanate (Eq. 139). This resistance allows selective removal of other

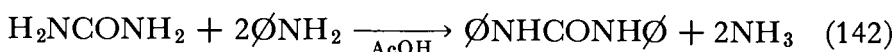
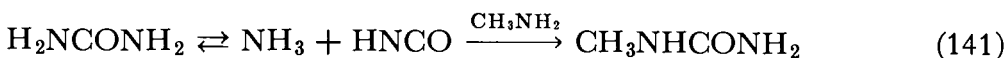


hydrolyzable groups from a thiourea moiety (Eq. 140).



Nucleophiles Nucleophiles in general have little effect on ureas, although amines will usually exchange with the amide groups on heating,

producing new ureas (Eqs. 141–143). These reactions apparently pro-



ceed through dissociation of the urea into cyanic acid or isocyanates, followed by recombination involving the introduced amine. It is a preparatively useful reaction with urea as starting material.¹³³

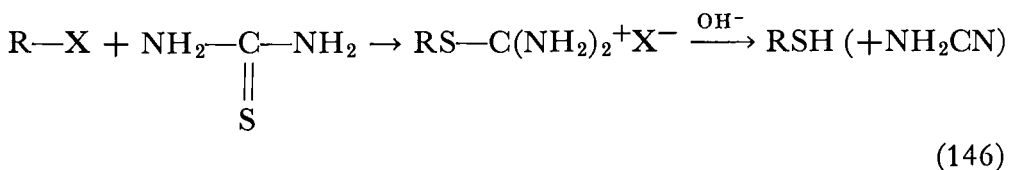
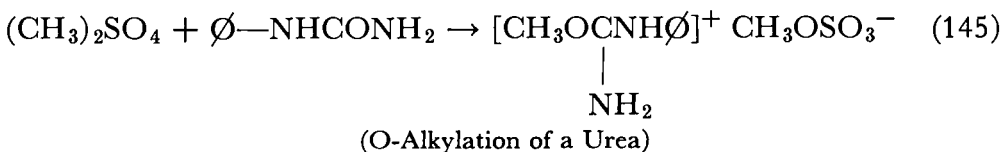
Isoureas undergo exchange of alkoxy groups when heated with alcoholic alkoxides, apparently through elimination to a carbodiimide or cyanamide and recombination.^{125b}

S-Alkylisothiuronium salts react with amines in a different way; the R—S—group is displaced, giving a mercaptan and a guanidine, in a smooth, preparatively useful reaction (Eq. 144). The guanidine



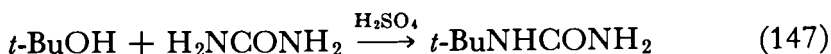
is apparently formed by addition of the amine to the free S-alkylisothiurea, followed by elimination, but when the medium is more acidic, such as when amine salts are used, dissociation first takes place into a mercaptan and cyanamide, which then combines with the amine.¹³⁴

Alkylation Alkylating agents attack ureas,¹³⁵ and more readily thio-ureas,¹³⁶ on O (or S), forming isourea or isothiuronium salts (Eqs. 145, 146). The reason for the avoidance of nitrogen must be sought in the

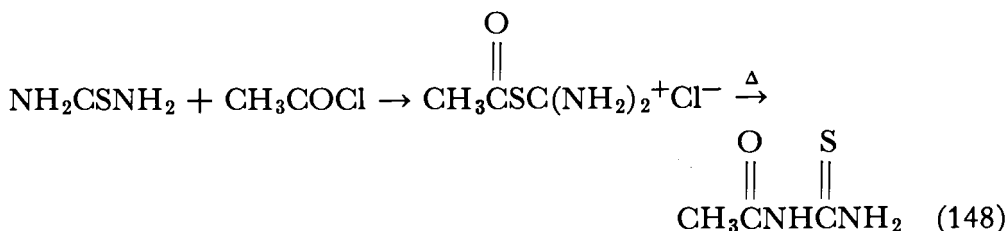


urea structure itself, and not simply in relative nucleophilicities, for oxygen is usually less nucleophilic than nitrogen in analogous situations. The reactions of ureas are actually parallel to those of amides and thionamides in this respect (see Chapter 4), and even to amidines, in all of which the doubly bonded atom is preferentially attacked by alkylating agents. Thiourea will react in this way with most alkyl halides, sulfates, or sulfonates,¹³⁶ and the products are often then used to generate mercaptans by converting them to the easily decomposed free bases (Eq. 146). In

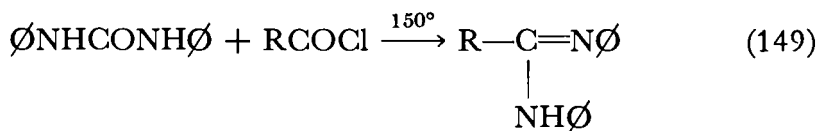
contrast, under the very different conditions of a tertiary alcohol in concentrated sulfuric acid, urea can be converted to *N-t*-butylurea in preparatively useful yield (Eq. 147).¹³⁷



Acylation Ureas can be acylated with acid chlorides or anhydrides to produce acyl ureides,¹³⁸ RCONHCONH_2 (Eq. 148), which are just



a form of diacyl imide. It may be that the acyl group is first added to oxygen, and then rearranges, for with thiourea the analogous stages can actually be isolated.¹³⁹ It is interesting that *N*-methylurea is acylated by acetyl chloride on the unsubstituted nitrogen, even though it would be expected to be the least basic, and, indeed, it may be that initial acylation occurs on oxygen, and is then followed by Chapman rearrangement. Strong heating of *N,N'*-diaryl ureas with acid chlorides (temperatures *ca.* 150°) results in a quite different reaction, however; amidines are formed in preparatively useful amounts¹⁴⁰ (Eq. 149). Tetra-



(Dains Amidine Synthesis)

alkyl ureas undergo replacement of oxygen by chlorine when treated with phosgene^{91b}; the products are versatile intermediates (Eq. 150).



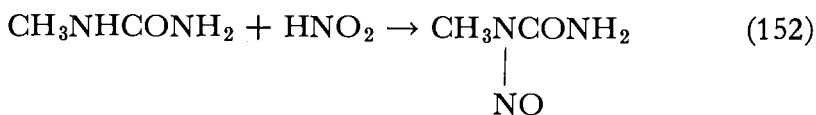
Similarly, phosphorus pentachloride converts trisubstituted ureas to chloroformamidines.^{125b}

Ureas can be both nitrosated and nitrated. Unsubstituted urea reacts with nitrous acid to produce nitrogen and carbon dioxide, a reaction of use in destroying excess nitrous acid in diazotization (Eq. 151).

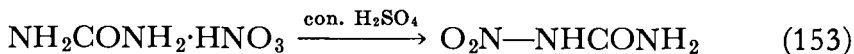


N-Alkyl ureas, on the other hand, nitrosate at the substituted nitrogen,

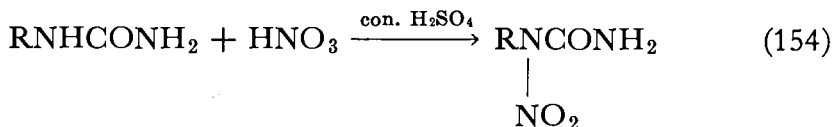
giving N-nitroso-N-alkylureas¹⁴¹ (Eq. 152), useful in the preparation of



diazoalkanes by reaction with base, and of hydrazines (by reduction). Nitration of unsubstituted urea can be carried out so as to produce nitrourea, mp 159°, by treating urea nitrate with concentrated sulfuric acid (Eq. 153). It dissociates readily into nitramide, O_2NNH_2 , and

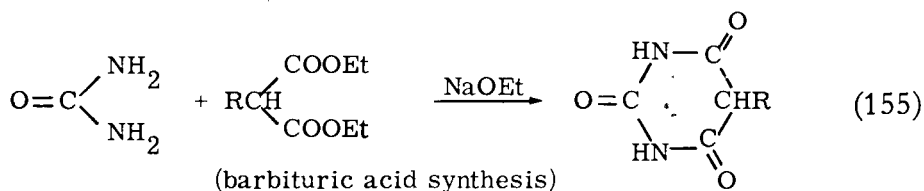


cyanic acid, and is a useful source of these substances. N-Alkyl ureas react with nitric acid in sulfuric acid to form N-nitro-N-alkyl ureas¹⁴² (Eq. 154).

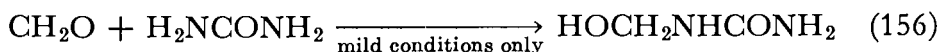


The reaction of phosphoryl chloride with urea apparently involves acylation at the oxygen atom, forming an addition product that reacts readily with amines to produce guanidines.¹⁴³ Phosphorus trichloride condenses phenylurea to phenylbiuret.

Acylation of ureas may be accomplished with esters under catalysis by sodium alkoxides; it appears likely that the ureide anion is the active agent. The most important application of this reaction is the reaction with malonic esters,¹⁴⁴ which produces cyclic ureides by acylation at both nitrogens (Eq. 155). The products are barbituric acids (triketopiperimides), of which many are valuable drugs with hypnotic action.

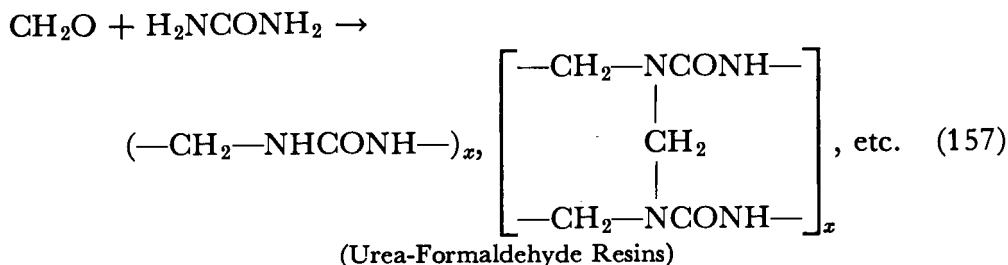


Aldehydes and Ketones The reaction of aldehydes and ketones with ureas¹⁴⁵ is essentially the same as their reaction with amides. An N—H moiety adds to the carbonyl carbon, forming at first carbinolamine derivatives, such as methylolurea (Eq. 156). Such substances



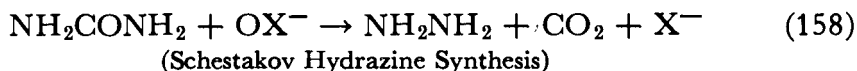
readily react further, however, with the elimination of water and formation of a new C—N bond with another urea molecule. Since urea itself has two amino groups, polymeric molecules can be built up in this way, with

cross links between the chains, both hydrogens of an amino group becoming involved (Eq. 157). This is the basis of the industrially important



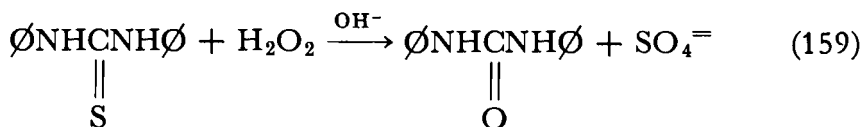
urea-formaldehyde resins.¹²⁰ Acetone gives "triacetone diurea," $(\text{CH}_3)_2\text{C}[\text{NHCON}=\text{C}(\text{CH}_3)_2]_2 \cdot 3\text{H}_2\text{O}$.

Oxidation The urea structure is relatively resistant to oxidation, and such reaction as occurs is usually a consequence of the reactivity of a substituent. Hypohalite, however, attacks ureas much as it does amides, giving at first N-halo compounds. In the case of urea itself, hydrazine is ultimately produced¹⁴⁶ (Eq. 158), if precautions are taken to see that



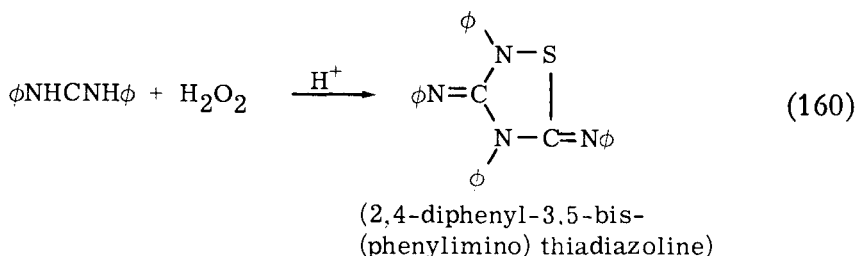
it is not destroyed by further reaction with hypohalite. The reaction is used for the industrial production of hydrazine, but it is not certain whether hydrazine is formed by a Hofmann rearrangement of the N-halo-ureide anion, or whether the process involves the bimolecular attack of —NH—X on —NH_2 , parallel to the Raschig synthesis of hydrazine from chloramine and ammonia.

Thioureas and S-alkylthioureas are readily oxidized at the sulfur atom, to give several types of products, depending both on the oxidizing agents and the initial substance. Thiourea is converted by hydrogen peroxide to guanylsulfinic acid,¹⁴⁷ which is probably a zwitterion, $^-\text{O}_2\text{SC}(\text{NH}_2)_2^+$, or to diguanyl disulfide, $\text{HN}=\text{C}(\text{NH}_2)\text{S—SC}(\text{NH}_2)=\text{NH}$, depending on the proportions. Alkaline peroxide converts thioureas essentially quantitatively to ureas, the sulfur being removed as sulfate (Eq. 159).

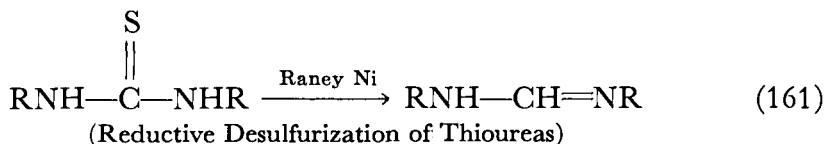


N-Phenylthioureas undergo cyclization when oxidized in acid solution,

however ¹⁴⁸ (Eq. 160). The course of the reaction, which involves two molecules of thiourea, has not been elucidated, but it is obvious that here, too, attack must be on sulfur. S-Alkyl thioureas are oxidized to alkane sulfonyl halides by chlorine or bromine, a reaction of preparative value.¹⁴⁹ Since chlorine may also attack the amino groups, converting them to highly explosive NCl₃, bromine is the preferred oxidizing agent.



Ureas are relatively resistant to reduction, but thioureas are susceptible to reductive desulfurization by Raney nickel ¹⁵⁰; the products are formamidines (Eq. 161).



PREPARATION ¹⁵¹ By far the most widely used synthesis for ureas is the reaction of isocyanates or cyanic acid with ammonia or amines (Eqs. 162–164) (see Part 2). Where it is applicable, it is an excellent method, and



it can be adapted to the preparation of mono-, di-, and trisubstituted ureas. The corresponding reactions leading to thioureas (Eq. 165) are



also useful synthetically,¹⁵² although they are slower, and in most cases reach equilibrium noticeably short of completion. There is sometimes

advantage in using nitrourea as the source of cyanic acid,¹⁵³ in place of potassium cyanate.

Carbamyl chlorides, obtainable from amines and phosgene, can also be used to prepare a wide variety of ureas by reaction with ammonia or amines.¹⁵⁴ Tetrasubstituted ureas can be prepared in this way (Eq. 166).



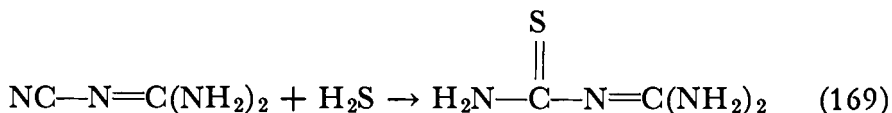
Substituted ureas can often be obtained by exchange reactions between amines and other ureas; the reaction of aliphatic primary amines with unsubstituted urea to give monoalkyl ureas is a particularly useful application¹³³ (Eq. 167).



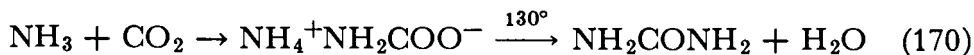
Although ureas are formed readily by the hydration of carbodiimides and cyanamides (Eq. 168), such reactions are rarely of preparative signifi-



cance, owing to the limited accessibility of the starting materials. An exception is the industrial production of urea itself from calcium cyanamide.¹²⁰ The reaction of dicyandiamide with hydrogen sulfide, which adds to the cyanamide moiety of the molecule, is a useful synthesis for guanythiourea¹⁵⁵ (Eq. 169).



Direct combination of carbon dioxide with amines can give ureas under the influence of heat and pressure, but is not generally important except in the case of the industrial preparation of urea¹²⁰ (Eq. 170). The



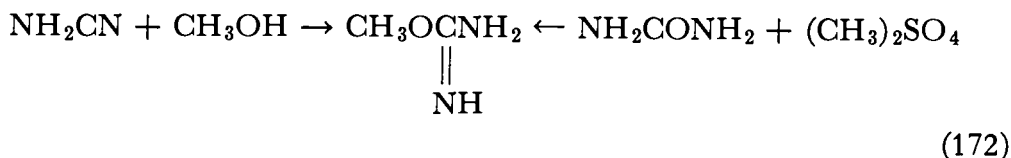
corresponding reaction with carbon disulfide proceeds more readily, especially with anilines, and is a useful synthesis for symmetrical diarylthioureas¹⁵⁶ (Eq. 171). The same result is accomplished by thiophos-



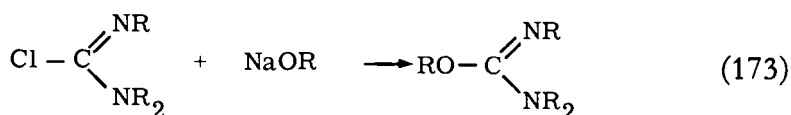
gene¹⁵⁷; thiocarbamyl chlorides are isolable intermediates. Unsymmetrical thioureas are sometimes conveniently prepared by the addition of hydrogen sulfide to cyanamides.⁷⁶

Isoureas can be formed by the direct alkylation of ureas, but have

more commonly been made by the addition of alcohols to cyanamides and carbodiimides ^{77, 125b} (Eq. 172). Isoureas can also be prepared



satisfactorily by the reaction of chloroformamidines with sodium alkoxides (Eq. 173). S-Alkylisothioureas must be prepared by alkylation of thio-



ureas (Eq. 174), or by addition of mercaptans to cyanamides.^{77b}



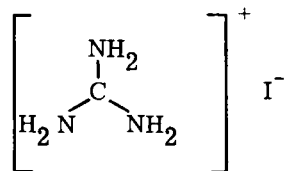
C. Guanidine and Derivatives

NOMENCLATURE Guanidines are almost invariably named as substituted derivatives of guanidine itself. The locants N,N',N'' are commonly used to designate the positions when more than one substituent is present, but some indexers (notably *Chemical Abstracts*) prefer to use the numbers 1,2,3, in which position 2 is the double-bonded N. When there is only one substituent, a locant is not necessary, since tautomers of the types $\text{RN}=\text{C}(\text{NH}_2)_2 \rightleftharpoons \text{RNHC}(\text{NH}_2)\text{NH}$ equilibrate too rapidly to allow separate characterization. The prefix "guanidino," for $\text{H}_2\text{NC}(=\text{NH})\text{NH}-$, is used in cases where naming the substituent on guanidine would be awkward or would misplace the desired emphasis; e.g., guanidinoacetic acid, $\text{H}_2\text{NC}(=\text{NH})\text{NHCH}_2\text{COOH}$. This prefix should be carefully distinguished from "guanyl," which stands for the amidine grouping, $\text{H}_2\text{NC}(=\text{NH})-$, as in guanylacetic acid, $\text{H}_2\text{NC}(=\text{NH})\text{CH}_2\text{COOH}$, the half amidine of malonic acid.

PROPERTIES Guanidine itself is a very hygroscopic, colorless, crystalline solid, mp 50°, almost infinitely soluble in water. Because they are so very difficult to isolate from their salts, the smaller alkylguanidines are almost never prepared as the free bases, and little is known of their physical properties. Pentamethylguanidine is a liquid, bp 155–160°. Nitroguanidine, mp 232°, is an explosive; nitrosoguanidine, yellow needles, mp. 160–165°, is also known.

Guanidine is a remarkably strong base; K_b has been estimated as 3×10^{-1} ($\text{p}K_a = 13.65$), making it the strongest organic base barring the quaternary ammonium hydroxides. Alkylguanidines share this property; their solutions are strongly basic, and they form very stable salts.

Even aryl and acyl guanidines are basic enough to dissolve in aqueous mineral acid. In salt formation, the proton is added to the dicoordinate nitrogen, forming a trigonally symmetrical cation, as shown by the X-ray diffraction of guanidinium iodide,¹⁵⁸ in which all three nitrogens are seen to be equivalent. Although the cation can also be represented as an



(symmetrical structure of guanidinium iodide)

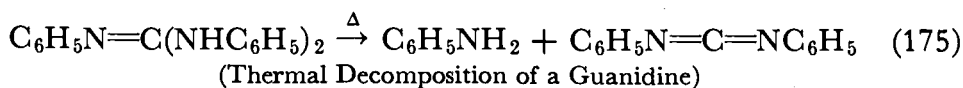
immonium ion with a double bond to any of the three nitrogens, the "carbonium" ion structure represents its symmetry properties more simply. Both types of structure are implicit in the concept of a delocalized π orbital derived from a p orbital of carbon and of each nitrogen.

Guanidine is a completely ammonolyzed carbonic acid, as was emphasized in the crusading work of E. C. Franklin¹⁵⁹ in the 1920's, and might be expected to function as an acid in a basic enough environment. Sodium hydride is sufficient, and guanidine reacts with it as a dibasic acid, forming the salts $\text{NaH}_2\text{NC}(\text{NH})_2$ and $\text{Na}_2\text{C}(\text{NH})_3$. Acylation naturally increases the acid strength of guanidine, and nitroguanidine is actually acidic in water solution.

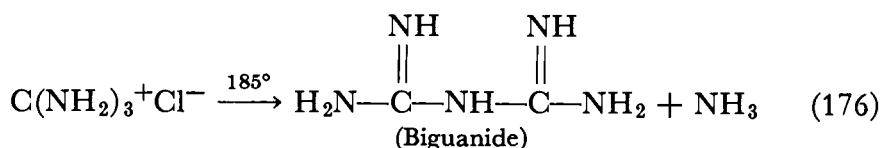
Several guanidine derivatives occur in nature; e.g., creatine, $\text{HOOC-CH}_2\text{N}(\text{CH}_3)\text{C}(=\text{NH})\text{NH}_2$, its N-phosphonic acid phosphocreatine obtained from muscle extracts, and arginine (δ -guanidino- α -aminobutyric acid). N-Methylguanidine, which is found in partially rotted flesh, is presumably a decomposition product of creatine.

REACTIONS Salt formation with acids is a particularly well-developed reaction of guanidines, and guanidine even forms a well-defined carbonate. A large number of guanidines are known only as their salts, which are invariably monobasic, although there are three nitrogen atoms. The addition of a second proton would, of course, break up the delocalized π orbital so that it could no longer encompass all three nitrogens, and would thereby cause a loss of stabilization.

Heating causes decomposition of guanidines.¹⁶⁰ The first step appears to be an elimination reaction, giving an amine and a carbodiimide or cyanamide (Eq. 175); secondary products may in turn arise from these. Attempted distillation of *sym*-triphenylguanidine, for example, gives

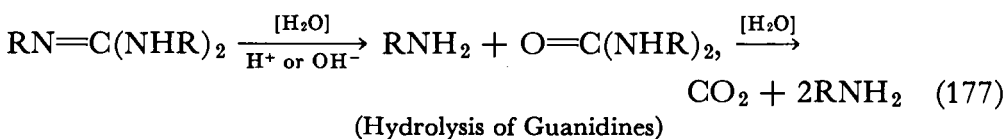


aniline and diphenylcarbodiimide, which is the reverse of a general reaction by which guanidines are formed. When guanidine hydrochloride is heated, biguanide is formed (Eq. 176). This substance, like biuret,

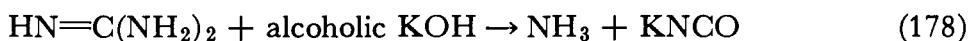


forms complexes with many metal ions.¹³⁰

Hydrolysis of guanidines is catalyzed by either acid or base, but is generally slow enough to require extensive heating. Ureas are the first stage in the hydrolysis, and can often be isolated; complete hydrolysis gives carbon dioxide and ammonia or amines (Eq. 177). Hydrolysis of



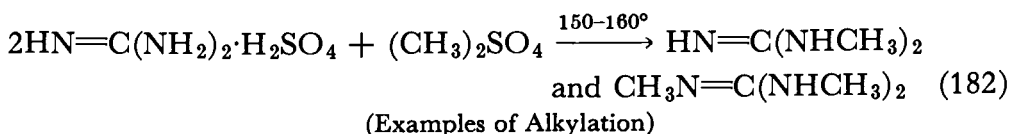
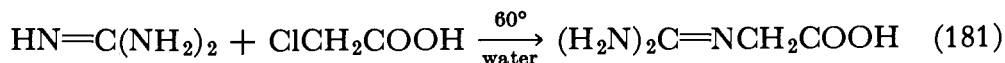
this sort clearly involves attack of a nucleophile (H_2O or OH^-) on the guanidine carbon; however, under strongly basic conditions, a proton may be removed first, causing decomposition to follow a different path, resulting in cyanate or cyanamide¹⁶¹ (Eqs. 178, 179). Mild nucleophiles



do not react with guanidines readily, but hydrazine, if used in excess, will replace all three amino nitrogens, one by one, producing the hydrazine analogue, triaminoguanidine (Eq. 180).¹⁶²

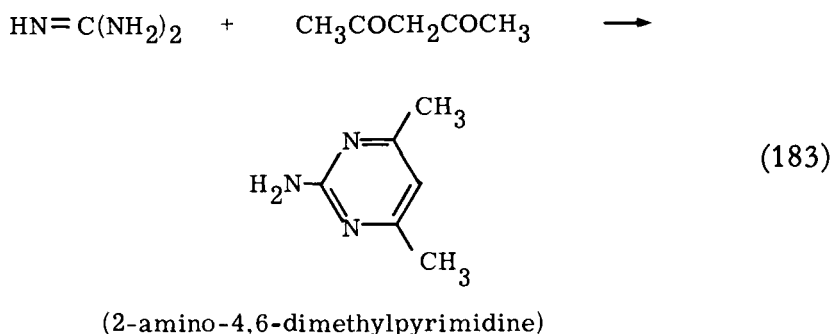


Alkylation can be brought about by reaction of the usual reagents with guanidines (or their salts in alkaline solutions)¹⁶³; at temperatures high enough, guanidine salts can be alkylated without the presence of a base¹⁶⁴ (Eqs. 181, 182). Little use has been made of these reactions.

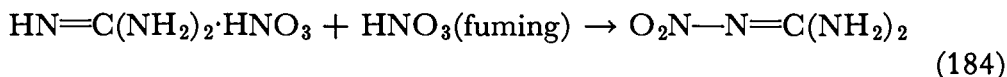


Pentamethylguanidine is converted by methyl iodide to hexamethylguanidinium iodide, $\text{C}(\text{NMe}_2)_3^+\text{I}^-$.

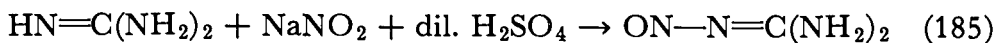
The reactions of aldehydes and ketones with guanidines are of principal importance when a ring can be closed involving two of the guanidine nitrogens. With 1,2-bifunctional compounds, such as α -halo ketones, five-membered rings (imidazole derivatives) are formed, and with 1,3-bifunctional compounds, six-membered rings are produced (pyrimidine derivatives) (Eq. 183). These reactions have seen much application in synthesis.¹⁶⁴



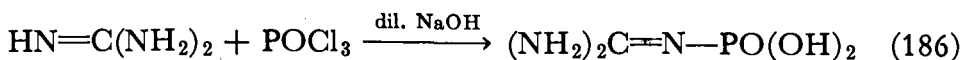
Guanidines have been acylated by a variety of acylating agents, both organic and inorganic. Fuming nitric acid gives nitroguanidine¹⁶⁵ (Eq. 184), but the reaction followed with nitrous acid depends very much on the



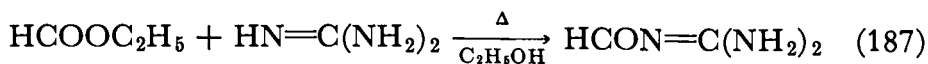
conditions. Nitrosoguanidine can be isolated from the reaction with sodium nitrite and dilute sulfuric acid in the cold¹⁶⁶ (Eq. 185), but reac-



tion can proceed further, with complete destruction of the guanidine system and conversion of the amino groups to nitrogen. Cyanamide has also been obtained. Guanidine has been phosphorylated with phosphorus oxychloride,¹⁶⁷ producing a compound of considerable biochemical interest (Eq. 186).

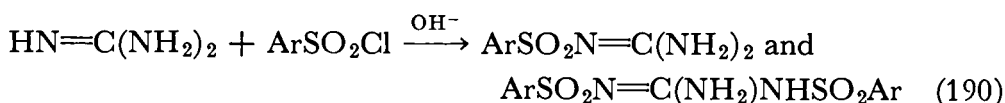
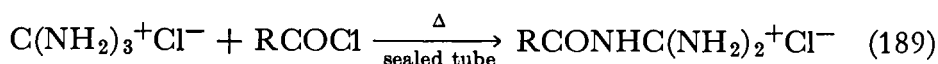
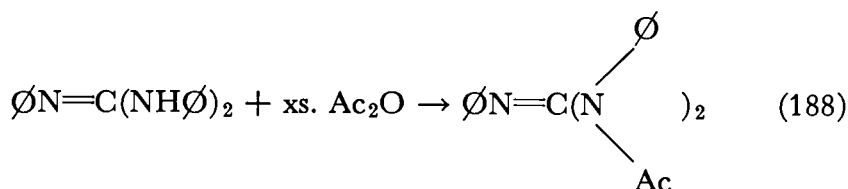


Esters will react with free guanidine when heated, producing mono-acyl derivatives¹⁶⁸ (Eq. 187). Acid anhydrides and chlorides will also

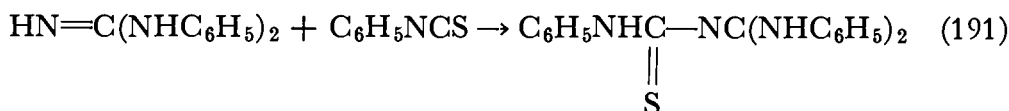


acylate guanidine salts, particularly the carbonate, even in the absence

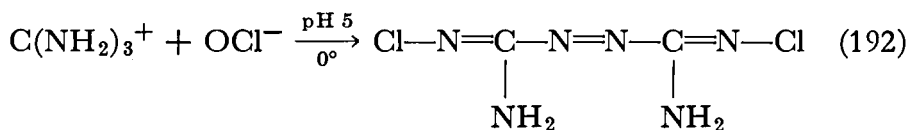
of added base ¹⁶⁹ (Eqs. 188–190). Although monoacyl derivatives are



the usual products, diacyl derivatives may be produced. Isocyanates, isothiocyanates, and carbodiimides also act as acylating agents toward guanidines ¹⁷⁰ (Eq. 191).

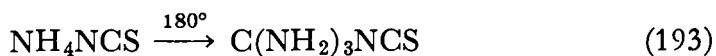


Although guanidine and its derivatives are not active reducing agents, they will react with many strong oxidizing agents. The nitrogens are attacked, and may be converted to nitrogen, nitrous oxide, nitric acid, or to azo compounds ¹⁷¹ (Eq. 192). Hypohalites may act as oxidizing

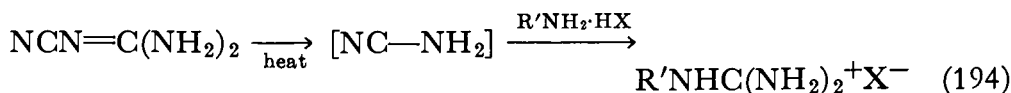


or halogenating agents, producing N-chloro- or N-bromoguanidines, for example. ¹⁷² The guanidine system is not easily reduced, and guanidine salts are not hydrogenated under ordinary conditions.

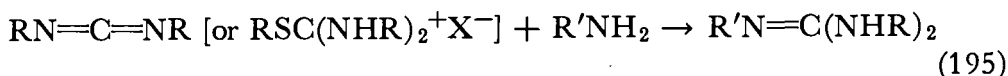
PREPARATION The simplest preparation of guanidine is perhaps the heating of ammonium thiocyanate. Although the first product (and the only one at lower temperatures) is thiourea, at higher temperatures guanidine thiocyanate is formed in good yield ¹⁷³ (Eq. 193). Another



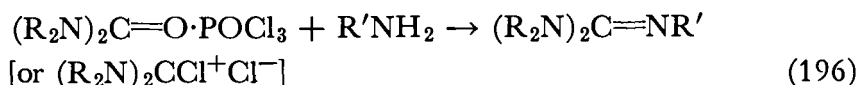
simple synthesis is fusing dicyandiamide (obtained from calcium cyanamide) with ammonium salts ¹⁷⁴ (Eq. 194). This is, of course, really a



reaction of cyanamide, formed from dicyandiamide on heating. When amine salts are used, substituted guanidines are produced. S-Alkylthiuronium salts are also convenient *in situ* sources of cyanamide or carbodiimides for guanidine synthesis¹³⁴ (Eq. 195). Guanidines are

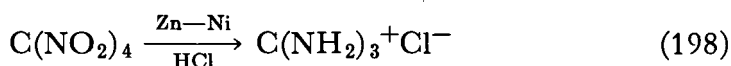
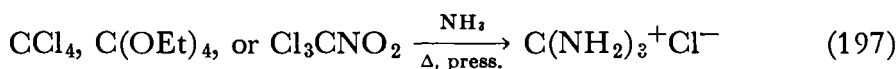


conveniently obtainable from ureas through chloroformamidinium chlorides, or their adducts with phosphoryl chloride, which react readily with amines^{91b, 143} (Eq. 196). The foregoing reactions constitute the



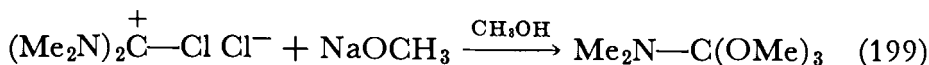
principal laboratory routes to guanidines.

Of minor importance are the ammonolysis of carbon tetrachloride, chloropicrin, or ethyl orthocarbonate,¹⁷⁵ and the reduction of tetranitromethane¹⁷⁶ (Eqs. 197, 198).

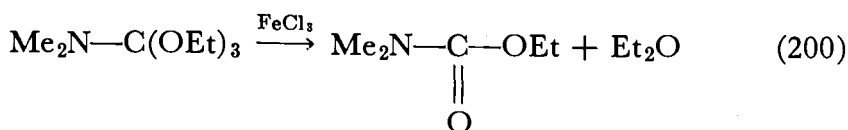


COMPOUNDS WITH TETRACOÖRDINATE CARBON

Nitrogen derivatives of carbonic acid with tetracoördinate carbon, which are thus amides of *orthocarbonic* acid, are known only with either one or two amino groups. Methyl dimethylamino-orthoformate, $\text{Me}_2\text{N}-\text{C}(\text{OMe})_3$, is a colorless liquid, bp 131–132°. It is prepared by the reaction of N,N,N',N'-tetramethylchloroformamidinium chloride with methanolic sodium methoxide^{91b} (Eq. 199). Such compounds

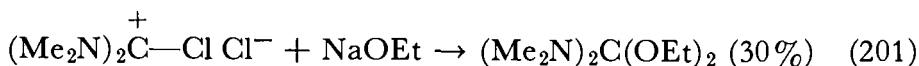


eliminate an ether to form urethans when treated with ferric chloride (or, presumably, other Lewis acids) (Eq. 200).

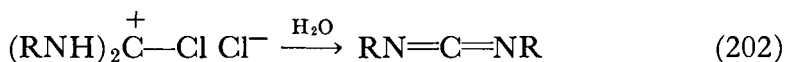


Tetramethylurea diethyl acetal (*bis*-dimethylaminodiethoxymethane), $(\text{Me}_2\text{N})_2\text{C}(\text{OEt})_2$, is a colorless oil, bp 61–65°/18 mm. It and analogous

compounds are formed from chloroformamidinium chlorides and dry (instead of alcoholic) sodium alkoxide (Eq. 201).^{91b}



The chloroformamidinium chlorides can also be considered as nitrogen derivatives of tetracoördinate carbon if the less probable covalent structure of a dichlorodiaminomethane, $(\text{R}_2\text{N})_2\text{CCl}_2$, is assumed for them; however, the tetramethyl derivative, for example, mp 162–164°, has the characteristics of an ionic compound. Not only tetrasubstituted, but even N,N'-disubstituted examples are known.^{91b} The tetrasubstituted compounds react principally through solvolytic replacement of the chlorines, and can give in addition to the aforementioned tetracoördinate alkoxy derivatives, guanidines, ureas, or thioureas by reaction with the appropriate nucleophile. The disubstituted compounds undergo elimination in contact with water, and give carbodiimides^{91b} (Eq. 202).



Guanidinium salts can likewise be considered formally as derivatives of tetracoördinate carbon, but the evidence against the covalent structure thereby implied is overwhelming.

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chapter
seven

Ammonia

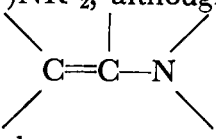
Derivatives of the Carbonyl Group:

Imines, Enamines, *gem*-Diamines,
and Carbinolamines and Their Esters

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INTRODUCTION AND NOMENCLATURE

The compounds discussed in this chapter are derivatives of the ketone and aldehyde oxidation state in which at least one bond of the carbon is to a nitrogen atom of the oxidation state of ammonia. The principal structures fitting this definition are $R_2C=NR'$, $R_2C(NR_2)_2$, and $RC(OR')NR'_2$, although others are obviously possible. Compounds of the

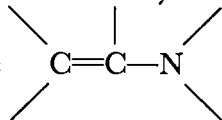
type  are also included, since their chemistry is so closely related.

Simple isoelectronic replacement of $=O$ by $=NH$ leads to the structure $\begin{array}{c} \diagup \\ C=NH \\ \diagdown \end{array}$, and to its N-substituted derivatives. As a class, such compounds are called imines, or more specifically, aldimines and ketimines, $RCH=NR'$ and $R_2C=NR'$. They are also sometimes called

"azomethines," since the term "azomethine group" for $\begin{array}{c} \diagup \\ C=N- \\ \diagdown \end{array}$ is a convenient analogue of "carbonyl group" for $\begin{array}{c} \diagup \\ C=O \\ \diagdown \end{array}$. Another widely used term for these compounds is "Schiff's base"; it is usually applied only to N-substituted imines, and is commoner in the older literature.

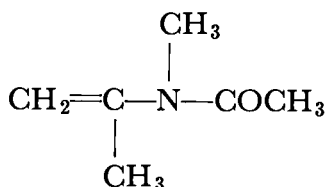
Individual imines are usually named after the corresponding aldehyde or ketone by the use of an additional separate word, as in "acetaldehyde methylimine," $CH_3CH=NCH_3$, or by use of the suffixes "-aldimine" and "-ketimine," as in N-methylacetalimine, or N-methyldiisopropylketimine, $CH_3N=C(CHMe_2)_2$. When imines are derived from aniline, they are usually named as anils, as in "benzophenone anil," $\phi_2C=N\phi$. With compounds derived from an especially complicated amine, or those in which a functional group on the amine moiety demands emphasis, the aldehyde or ketone moiety may have to be handled as a substituent, using the "-ylidene" suffix, as in "N-benzylidenesulfanilic acid," $\phi CH=N-C_6H_4-SO_3H$. Conversely, the amine moiety may be handled as a substituent, as in " α -phenyliminophenylacetic acid," $\phi-C(=N\phi)-COOH$. In certain cases, there may be advantage in naming imines as aza olefins, as in "2-azaperfluorobutene-2," $CF_3N=CFCH_3$. Imines of the type $RCH=N-CHR-N=CHR$ have acquired a system of trivial names, properly mystifying to the uninitiated, exemplified by "hydracetamide," $CH_3CH=N-CH(CH_3)-N=CHCH_3$, and "hydrobenzamide," $\phi CH=N-CH\phi-N=CH\phi$, and are even sometimes referred to by the class name "hydramides." Fully systematic names for these compounds are unwieldy, but "trimethylenediamines" is a useful compromise, from which is derived "tribenzylidenediamine" for hydrobenzamide.

Compounds having the structure



are commonly called

enamines, since they are the amine analogues of enols, although they can just as well be called vinylamines or alkenylamines. Individual compounds must be named in the latter way, as "2-methoxyvinyl-diphenylamine," $CH_3OCH=CH-N\phi_2$, or "N-isopropenyl-N-methylacetamide,"



Derivatives of the carbonyl oxidation state having a tetrahedral carbon must be named quite differently, since unsaturation implied in the foregoing names is absent. The compounds $\text{R}_2\text{C}(\text{NR}'_2)_2$ are usually called *gem*-diamines, although the term "aminal," falsely analogous to "acetal," has been suggested. Symmetrical derivatives, which comprise nearly all the known examples of this structural type, are named by the "-ylidene" nomenclature, as in "isopropylidene-*bis*-methylamine," $(\text{CH}_3)_2\text{C}(\text{NHCH}_3)_2$. Alternatively, one or both amino groups may be handled as substituents, as in "2,2-dianilino-3,3-dimethylbutane," $(\text{ONH})_2\text{C}-\text{C}(\text{CH}_3)_3$, or the aza system may be used, as in "3-methyl-

$\begin{array}{c} | \\ \text{CH}_3 \end{array}$
 2,4-diazaoctane," $\text{CH}_3\text{NHCH}(\text{CH}_3)\text{NH}(\text{CH}_2)_3\text{CH}_3$.

Compounds with an amino group and a hydroxyl group on the same carbon, $\text{R}_2\text{C}(\text{OH})\text{NR}_2$, are generally called as a class "carbinolamines"; the 1:1 addition compounds that ammonia or amines form with many aldehydes are believed probably to have this structure, but because of the uncertainty, they are often called by the noncommittal primitive nomenclature "aldehyde ammonia" or "aldehyde amine." Individual members are most simply named as α -amino alcohols or α -hydroxy amines, as in "2-aminopropanol-2," $(\text{CH}_3)_2\text{C}(\text{OH})\text{NH}_2$; however, derivatives of formaldehyde, which are especially often encountered, are commonly named by adopting the prefix "methylol" for the hydroxymethyl group, HOCH_2- , as in "N-methylolbenzamide," $\text{HOCH}_2-\text{NH}-\text{CO}\phi$.

The ethers of carbinolamines are named analogously as α -alkoxy amines, or α -amino ethers. In the special case of glycosides of amines, in which the sugar moiety has the hemiacetal structure, such compounds can be named in the same way as ordinary amines by use of the appropriate systematic name of the glycosyl group.

PROPERTIES

The smaller aliphatic imines without a substituent on the nitrogen are little known, for they polymerize extremely readily. No information at all is available about formalimine, $\text{CH}_2=\text{NH}$, and all reactions that might be expected to produce it lead instead to hexamethylenetetramine,

$(\text{CH}_2)_6\text{N}_4$, a type of *gem*-diamine. Acetaldimine has been reported as a mobile liquid, but not even a boiling point has been recorded, so readily does it change to a solid trimer. Benzaldimine is an unstable oil, bp $58^\circ/4$ mm.; benzophenone imine, mp 48° , and tribenzylidenetriamine (hydrobenzamide), mp 110° , are quite stable substances. N-Substitution increases the stability of imines considerably; although N-methylformaldimine is known only in the form of a trimer, N-ethylpropionaldimine, $\text{Et}-\text{N}=\text{CHEt}$, is a liquid boiling at 48° , quite close to the boiling point of hexane, and N-methylbenzaldimine boils at 180° , somewhat higher than propylbenzene. Anils, such as benzaldehyde anil, mp 54° , are usually solids.

Imines appear to be invariably weaker bases than the corresponding amines, although accurate measurements are few. *p*-Chlorobenzaldehyde anil, for example, has $\text{pK}_a = 2.8$, as compared to pK_a 4.6 for aniline. This result is ascribed to two competing effects.¹ The change from the amine structure to the imine structure involves a change in hybridization from sp^3 to sp^2 , which greatly lowers the basicity, whereas overlapping of the orbital holding the unshared electron pair with the π orbitals of the benzene ring, decreasing the basicity of anilines, is not possible in anils. This latter effect, which results in an increase of basicity of about 3 pK units, is not as great as the first, which can be estimated to be about 5 pK units from the fact that semicarbazones are weaker by about that amount than semicarbazide itself. The basicity of aliphatic imines has not been measured, since they are so rapidly hydrolyzed in acid solution.

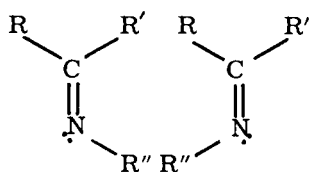
The $\text{C}=\text{N}-$ system is a weak chromophore, whose absorption lies in the ultraviolet. Conjugation with phenyl groups shifts the absorption toward the visible, but even benzophenone imine, λ_{max} 252 m μ , ϵ 1.75×10^4 , and its N-methyl derivative, λ_{max} 246 m μ , ϵ 1.54×10^4 , are colorless.² Anils of aromatic aldehydes and ketones are usually yellow, how-

ever. The infrared stretching vibration of the $\text{C}=\text{N}-$ system usually

falls at 1610–1635 cm^{-1} , and that of $\text{C}=\text{N}^+$ at 1665–1690 cm^{-1} .

The imine system has been found to be capable of geometrical isomerism, which means that the nitrogen atom must have sp^2 hybridization, the unshared electron pair being in a hybrid orbital. Interconversion of geometrical isomers is very easy in aliphatic imines, and geometrical isomers of them have not been isolated. Benzophenone imines can be isolated as separate isomers when one phenyl group is differently sub-

stituted from the other, however, although the isomers equilibrate rapidly in solution.³ A difference of 19 m μ has been observed between the ultra-violet maxima of *p*-chlorobenzophenone N-methylimine, the *cis* form absorbing at the shorter wave length. The ¹⁹F nuclear magnetic resonance of perfluoroacetone perfluoroisopropylimine, (CF₃)₂C=NCF(CF₃)₂, shows differentiated ketonic —CF₃ groups below 32°, above which the separate signals collapse, indicating interconversion too rapid for resolution.^{3b} This temperature indicates an activation energy of 13 kcal/mole, which is considerably less than that observed for aldoxime isomers, 25 kcal/mole.



(geometrically isomeric ketimines)

The simple aliphatic enamines unsubstituted on the nitrogen atom, R₂C=CH—NH₂, have not been isolated owing to their rapid tautomerization to the imine structure, but enamines in which the structure is fixed by substitution, R₂C=CH—NR₂, are well known. They polymerize readily, and are not stable to prolonged storage, although they can be stored for limited periods, preferably cold and under nitrogen. The smaller members are liquids, whose boiling points are not unlike those of saturated tertiary amines; dimethylvinylamine, for example, boils at 37–38°. Enamines are distinctly basic, and estimates from measurements in chloroform suggest that they are about one power of 10 weaker than the saturated amines with hydrogen in place of the vinyl groups, and thus slightly weaker than the corresponding tertiary amine. Aqueous acid hydrolyzes most enamines so rapidly that an accurate determination would be difficult.

The simplest stable primary enamine seems to be 2-aminopropenyl methyl ketone, CH₃COCH=C(CH₃)NH₂, derived from acetylacetone. It melts at 39° and boils at 214°. 2-Aminovinyl ketones are in general colorless, but have a maximum in the near ultraviolet at 300–350 m μ , with $\epsilon \simeq 10^3$. Completely unconjugated aliphatic enamines absorb in the ultraviolet^{4a} at $\lambda_{\max}$ 220–240 m μ , ϵ 4.2 — 9.9 $\times 10^3$; extended conjugation can shift the maximum far toward the visible,^{4b} of course. Infrared absorption^{4, 5} usually falls in the range 1622–1672 cm.⁻¹ mostly 1630–1660 cm.⁻¹. Enamine salts, which are actually imines, absorb at slightly higher frequencies, 1644–1691 cm.⁻¹, corresponding to C=N stretching. The structure of the salts of enamines as immonium salts,

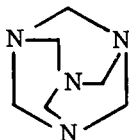
$\text{R}_2\text{CH}-\text{CR}=\overset{+}{\text{N}}\text{R}_2$, is indicated by the fact that compounds such as

neurine, in which the enammonium structure, $R_2C=CR-NR_3^+$, is fixed by substitution, do not absorb in the $1600-1700\text{ cm}^{-1}$ region.⁴ Preferential protonation at the β -carbon is in accord with various other physical and chemical properties of enamines, all of which point to an electron-rich double bond with enhanced electron density at the β -carbon. The vinyl hydrogen of cyclohexenylamines, for example, gives an nmr signal at 5.58τ , considerably upfield compared to the position of the vinyl hydrogens in cyclohexene (4.43τ).

Neurine, vinyltrimethylammonium chloride, is a naturally occurring quaternary enamine.

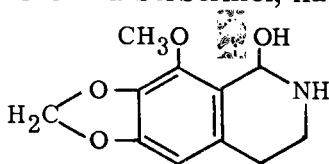
Simple *gem*-diamines are not stable unless both nitrogens are fully substituted, as would be expected on the basis of Erlenmeyer's rule. Their boiling and melting points are those normally to be expected of tertiary amines; *bis*(dimethylamino)methane, for example, is a liquid boiling at 85° . Hexamethylenetetramine, a rather special type of *gem*-diamine, is the best-known example; it is a solid, very soluble in water, and sublimes when heated strongly in vacuum. On the other hand, *gem*-diamines derived from aldehydes bearing an α -hydrogen usually eliminate a molecule of amine on distillation, giving an enamine. Hexamethylenetetramine is only a very weak base, a consequence to be expected in view of the inductive effect of one amino group on the other. Most *gem*-diamines are rapidly decomposed by aqueous acid, so that accurate determination of their basicity is not ordinarily possible.

gem-Diamines are colorless, and, of course, show no absorption in the double-bond region.



(hexamethylenetetramine)

Carbinolamines are known best as the N-methylol amide representatives such as $CH_3CONHCH_2OH$, mp 57° . Noncyclic carbinolamines, whether derived from aldehydes or ketones, are either very unstable or not known at all. "Acetaldehyde ammonia," presumably $CH_3CHOH-NH_2$, melts at $70-80^\circ$ with dissociation into acetaldehyde and ammonia, or into water and acetaldimine, which trimerizes. Cyclic carbinolamines are much more stable, however, and a number of naturally occurring substances, such as cotarnine and berberinol, have such a structure.



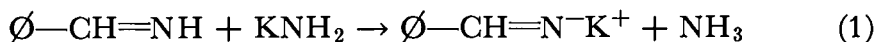
(cotarnine)

Carbinolamine ethers are much more stable than carbinolamines themselves, and the smaller ones can be distilled without decomposition, often at atmospheric pressure. They are usually oils, immiscible with water, and probably considerably weaker bases than ordinary tertiary amines, owing to the inductive effect of the oxygen. They are too rapidly hydrolyzed by aqueous acid for easy measurement of their basicity, however. The sulfur analogues, R_2NCH_2SR' , of carbinolamine ethers have similar properties.

REACTIONS

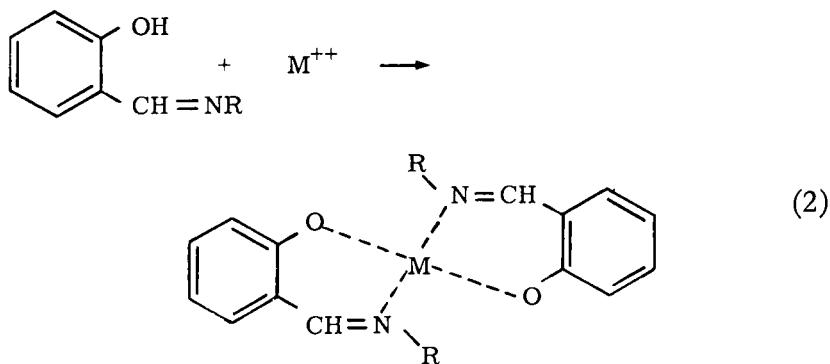
A. Ketimines and Aldimines

Imines form salts normally with the mineral acids, although such salts are often difficult to prepare or handle in water solution because of acid-catalyzed hydrolysis. Even in alcohol there may be difficulty, for some aldimine hydrochlorides have been observed to undergo alcoholysis readily. In the absence of hydroxylic solvents, however, imine salts can be very stable, and benzophenone imine hydrochloride, for example, sublimates at $230\text{--}250^\circ$ without decomposition. Unsubstituted imines are capable of forming salts with bases also, for the $=NH$ moiety has a weak latent acidity. Magnesium and lithium salts are well known, for they formed in the addition of organometallic reagents to nitriles (see "Preparation"). Benzaldimine forms a potassium salt when treated with potassium amide (Eq. 1). Water hydrolyzes the salts to the free imines com-



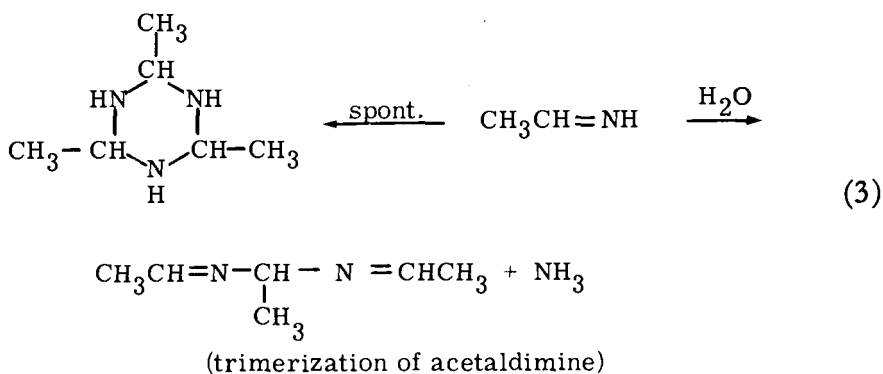
pletely, of course.

Imines form complexes, both ordinary and chelate, with many heavy metal ions⁶ (Eq. 2). These complexes are of importance in catalysis



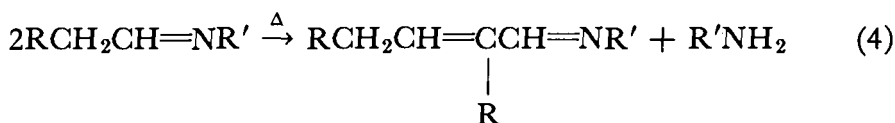
and in the analytical chemistry of metals.

The stability of imines to heat varies enormously. Three distinct types of reaction are observed: simple trimerization to form hexahydrotriazines; trimerization by loss of ammonia to form trimethylene diamines; and condensation reactions in which new carbon-carbon bonds are formed.⁵ Aldimines are understandably the most reactive. Salts of

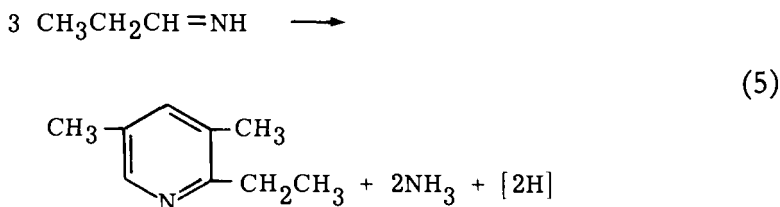


imines are usually less prone to undergo these reactions.

Carbon-carbon condensations of the aldol type often occur if there is an α -methylene group. When there is no substituent on the nitrogen,

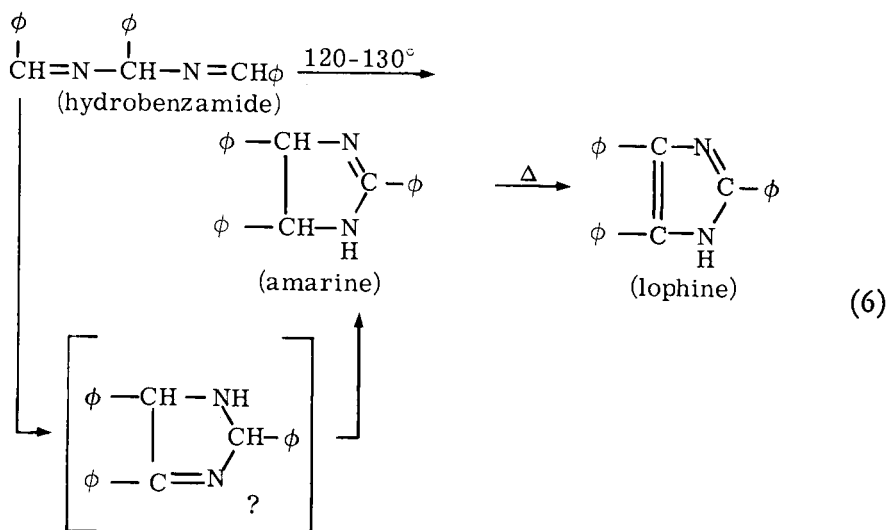


condensation may continue until a pyridine is formed (the way in which the concomitant oxidation occurs has not been clearly established) (Eq. 5).



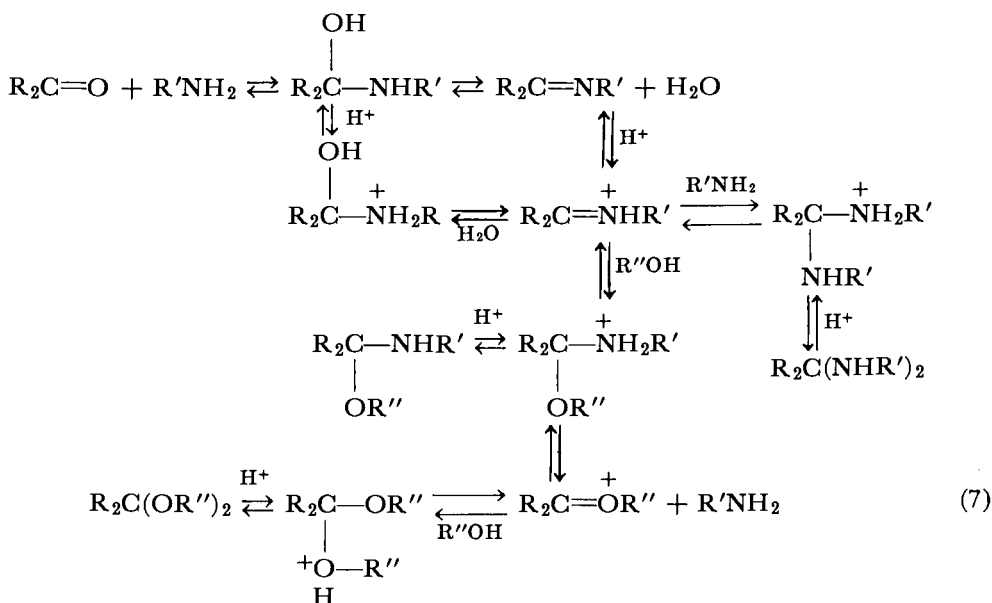
Benzaldimine forms tribenzylidenediamine (hydrobenzamide) even at room temperature, but more severe heating leads to carbon-carbon condensation (Eq. 6). At 120–130°, a crystalline base called amarine is formed; it was identified after many years as a triphenylimidazoline. At higher temperatures, another base, called lophine, is formed. It is 2,4,5-triphenylimidazole, and results from loss of hydrogen from amarine. Strain^{5c} has suggested that these substances arise through an ammono analogue of the benzoin condensation.

Imines react with all varieties of nucleophiles in much the same way as do aldehydes and ketones, although there are some significant differ-



ences in ease of reaction. Addition reactions are often found to be acid-catalyzed.

The solvolytic reactions of imines inevitably involve the closely related systems with tetrahedral carbon, the *gem*-diamines, carbinolamines, etc. These types of compounds are very easily interconverted, especially in the presence of acid, and it is not always simple to distinguish whether an observed reaction is actually characteristic of the class of substance initially selected by the chemist for study, or of one of its solvolytic transformation products. The solvolytic chemistry of aldehyde-amine compounds has been reviewed and correlated by Wagner ^{5d}; the principal transformations are outlined in the adjacent scheme (Eq. 7). The available evidence



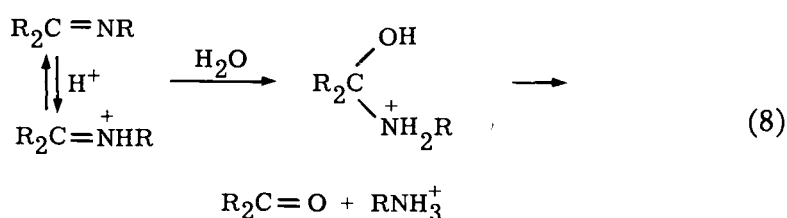
(Solvolytic Relationships among Imines and Other Carbonyl Derivatives. R May Be Any Combination of H, Alkyl, or Aryl)

indicates that all the reactions proceed by eliminations and additions, and not by bimolecular nucleophilic displacement.

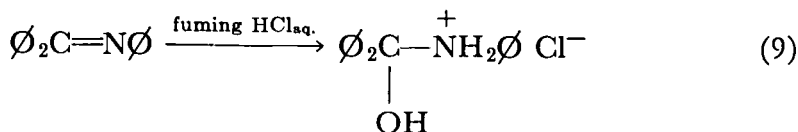
Hydrolysis shows a rate dependence on the first power of $[H^+]$, and is also subject to general acid catalysis.⁷ Although the eventual products are an aldehyde or ketone and an amine, a carbinolamine (or its conjugate acid) is certainly an intermediate stage, whose steady-state concentration may be appreciable. In fact, many anils give isolable carbinolamine hydrochlorides when treated with cold fuming hydrochloric acid. The ease of hydrolysis varies enormously with structure, with half lives from a few seconds with some aliphatic imines to immeasurably long with hindered benzophenone imines. Base catalysis of hydrolysis is relatively

ineffective, except for ternary immonium compounds, $R_2C=NR_2^+$, which combine rapidly with hydroxide ion to give carbinolamines⁸; the rate

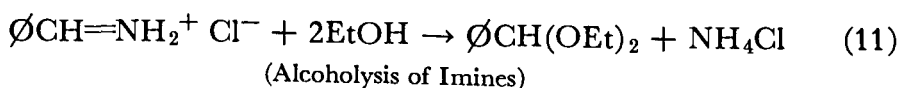
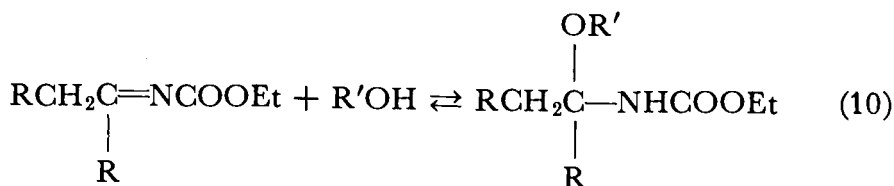
law in base,^{7c} $-d(R_2C=NR)/dt = k(OH^-)(R_2C=NHR)^+$, implies that



the conjugate acid, which is the active species, is destroyed by increasing base concentration.

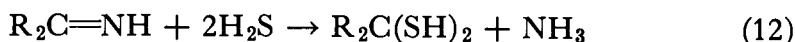


Alcoholysis of imines occurs in two stages, the first being reversible addition to form a carbinolamine ether.⁹ Acid catalyzes further alcoholysis to yield an acetal and an amine salt.¹⁰ Hydrogen sulfide reacts

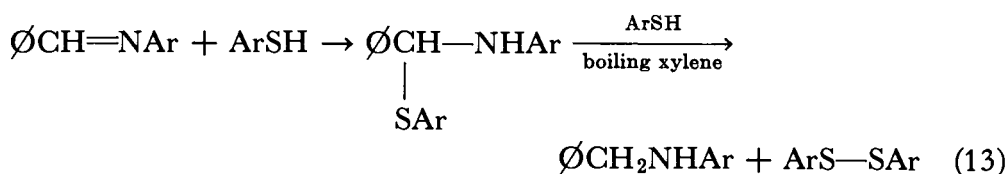


analogously, without the necessity for additional acid catalysis, giving

gem-dithiols in preparative yields ^{11a} (Eq. 12). Mercaptans, however,

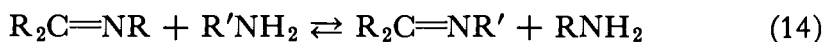


simply add, forming α -amino thioethers (Eq. 13), unless the reactants

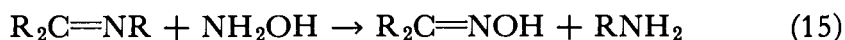


are heated too high, in which case the imine is reduced to an amine at the expense of the mercaptan ^{11b} (Eq. 13).

The reaction of imines with primary amines usually results in exchange,¹² transalkylidenation, which comes to an equilibrium unless one amine is removed by distillation (Eq. 14). Acid catalysis is not required.



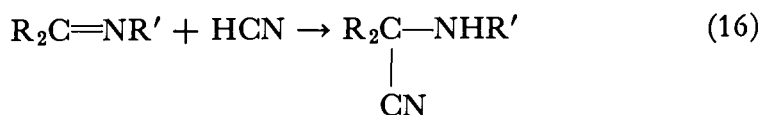
Only rarely has the intermediate *gem*-diamine been isolated.¹³ The reaction with hydrazines bearing an NH_2 group follows the same course, but equilibrium is far on the side of the hydrazone. An interesting characteristic of the reaction is that hydroxylamine and hydrazines react very much faster with imines than with the corresponding ketone (or aldehyde).¹⁴ As a result, the formation of oximes and hydrazones from



carbonyl compounds is catalyzed by aniline, which rapidly converts aldehydes and ketones to anils as the first step.

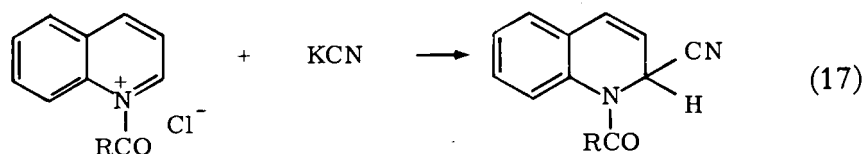
Sulfurous acid adds to many imines ^{5d,e} to give products that are internal salts of α -amino sulfonic acids $RNH_2-CR_2-SO_3^-$. The corresponding sodium salts do not appear to be as stable, for sodium bisulfite sometimes fails to add in cases where sulfurous acid does.

The addition of hydrogen cyanide to imines is closely related to the foregoing solvolytic reactions. It usually occurs readily, giving α -amino nitriles, analogous to the formation of cyanohydrins ^{5c, 15} (Eq. 16). It is

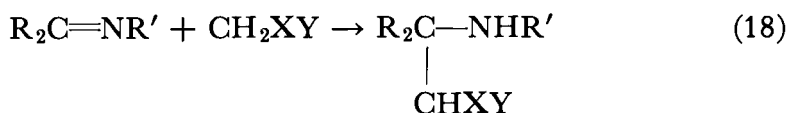


the basis of the Strecker synthesis of α -amino acids. In the special case of *N*-acyl quinolinium and isoquinolinium salts, where the azomethine

group is part of a ring system, cyanide addition also occurs, giving α -cyano dihydro derivatives. It is then known as the Reissert reaction ¹⁶ (Eq. 17).

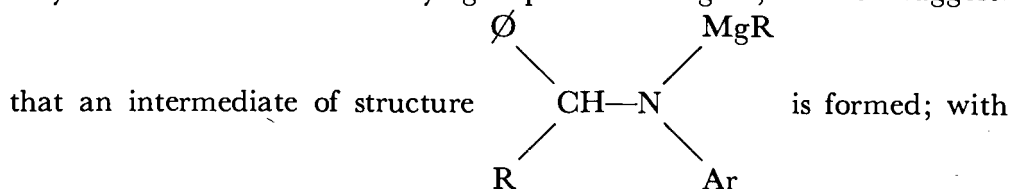


Active hydrogen compounds add to imines substituted on the nitrogen in qualitatively the same way as they do to carbonyl compounds ¹⁷; the products are amines (Eq. 18). Metal derivatives of active methylene

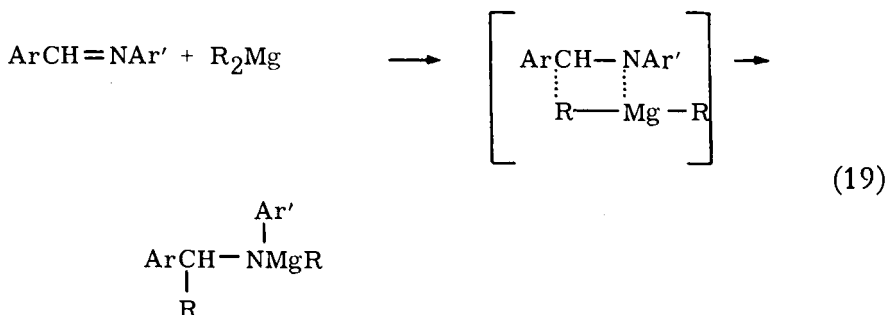


compounds add similarly.¹⁸ These additions are sometimes sluggish compared to the reactions of aldehydes and ketones, and require several hours for completion. Immonium salts, when they are stable in the presence of the carbanion provider, react much more readily ^{15b, 19}; such a reaction is one path for the familiar Mannich reaction,^{15d, 18} in which an amine, formaldehyde, and an active hydrogen compound form an amino-methylated product (see Chapter 2).

The addition of Grignard reagents to benzaldehyde anils consumes only half of the available alkyl group of the reagent,²⁰ which suggests



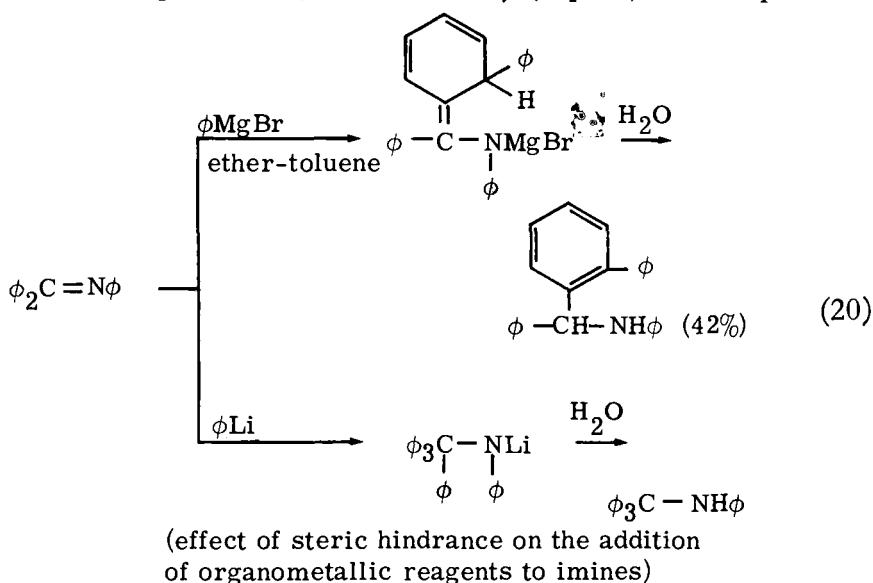
more reactive imines, all of the Grignard reagent may react, however. The kinetics conform to the rate law $v = k (\text{R}_2\text{Mg})(\text{imine})$, and the rate is not significantly affected by *para* substitution on either phenyl group of the anil. These observations are consistent with a four-center reaction mechanism (Eq. 19), but are inconsistent with the often postulated forma-



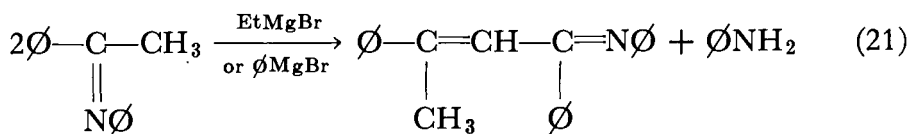
tion of an addition complex that only slowly goes over to the product.

Complex formation can occur, however, as in the case of benzophenone anil, which evolves heat when added to a solution of methyl-magnesium bromide, but is recovered unchanged on hydrolysis.²¹

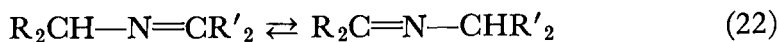
The addition of organometallic reagents to imines is subject to interference by steric hindrance and by the presence of enolizable hydrogens. Benzophenone anil, for example, reacts with phenylmagnesium bromide only under forcing conditions, and then undergoes 1,4-addition, involving an *ortho* position of the benzophenone moiety.²¹ Phenyllithium, which has smaller steric requirements, adds normally (Eq. 20). Acetophenone



anil, which has potentially enolizable hydrogens, adds neither ethylmagnesium nor phenylmagnesium bromide.¹⁴ Instead, dypnone anil, a product of an aldol-like condensation, is formed, apparently a consequence of an acid-base reaction with the Grignard reagent (Eq. 21).



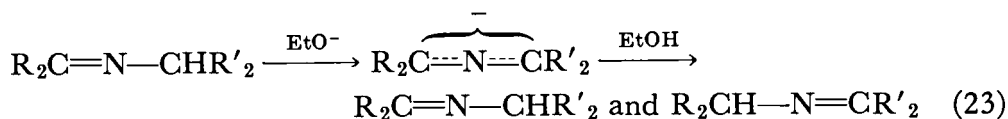
Bases may also bring about reactions of imines that are neither addition, condensation, nor solvolysis. The most important of these is prototropic shift of a hydrogen to give an isomeric imine (Eq. 22). This



reaction is of much biochemical importance, for it is the way by which transamination among α -amino acids and pyridoxal occurs. The isomerization is ordinarily negligibly slow, and tautomeric imines can be isolated and stored without difficulty. Strong bases, such as sodium

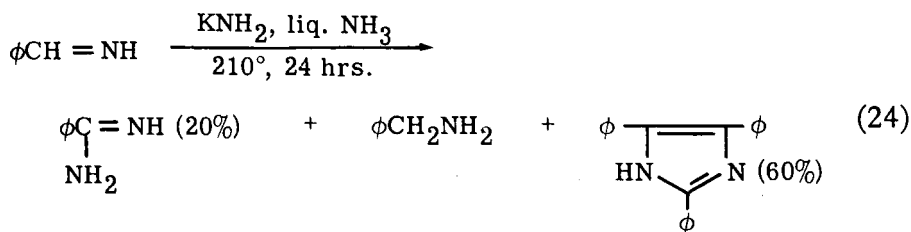
ethoxide, catalyze the reaction,²² and acid-strengthening substituents accelerate it. With *N*-benzyl benzaldimines, *p*-methoxy and *p*-dimethylamino substituents favor the isomer derived from the substituted aldehyde, whereas *p*-halo and *p*-methyl (sic!) substituents weakly favor the other.

The mechanism of the prototropic isomerization involves removal of a proton from the saturated α -carbon, generating a delocalized carbanion, which reaccepts a proton from the medium to give both isomerized and unisomerized imine (Eq. 23).

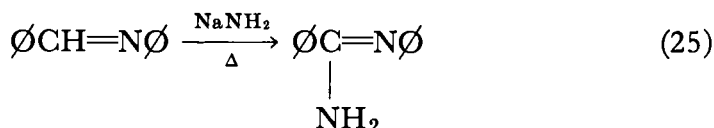


Initial studies with compounds of the type $\text{R}_2\text{C}=\text{N}-\text{CHRR}'$, in which the α -carbon of the amine substituent is the seat of optical activity, showed the rates of isomerization and racemization to be identical, and the initial rates of racemization and deuterium exchange with the solvent to be the same.²³ These observations appeared to be inconsistent with the intermediacy of a carbanion, and a concerted process was proposed, in which base (EtO^-) removes a proton from one carbon synchronously with the donation of a proton to the other carbon by the conjugate acid (EtOH). The rate of the isomerization was shown²⁴ to be first order in imine. The identities in the rates of the foregoing processes were subsequently shown to be fortuitous, the consequence of high ratios of isomerized to unaltered imine in the kinetically controlled re-protonation (or deuteration) of the carbanion. Indeed, with other systems, the rates of isomerization, racemization, and deuterium exchange have been found to be very different.²⁵ The intermediacy of carbanions is thus well established; whether the one-step synchronous mechanism also plays a role in suitable circumstances is an open question. The specific catalytic activity of imidazole in these reactions, as contrasted to other heterocyclic bases, such as morpholine, is also best interpreted by a concerted mechanism.²⁶

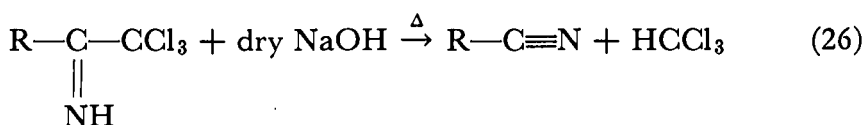
Another reaction brought about by base is the disproportionation of benzaldimine, which is converted into benzamidine, benzylamine, and much lophine when heated under pressure with potassium amide in liquid ammonia^{5c} (Eq. 24). The reaction has been interpreted as an



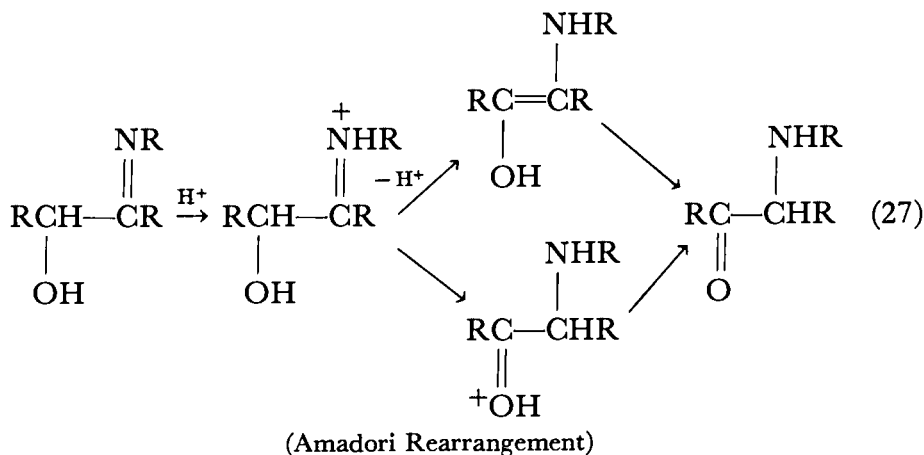
ammono analogue of the Cannizzaro reaction, but has not been further studied. The formation of N-phenylbenzamidine from benzaldehyde anil and sodamide has been reported ²⁷ (Eq. 25), but it is not clear whether



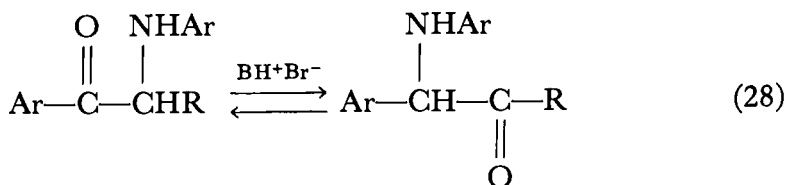
this product is the result of a Cannizzaro-type reaction or of an open-chain analogue of the Tschitschibabin amination of pyridine. When strongly electron-withdrawing groups are present, as in trichloromethyl ketimines, carbon-carbon cleavage can be accomplished by heating with strong base, giving nitriles ²⁸ (Eq. 26).



α -Hydroxy imines undergo a prototropic shift involving the hydroxy group, known as the Amadori rearrangement.²⁹ The rearrangement takes place in basic medium, but is accelerated by small amounts of acids. Rearrangement proceeds in moderate yield to α -amino ketones (Eq. 27).

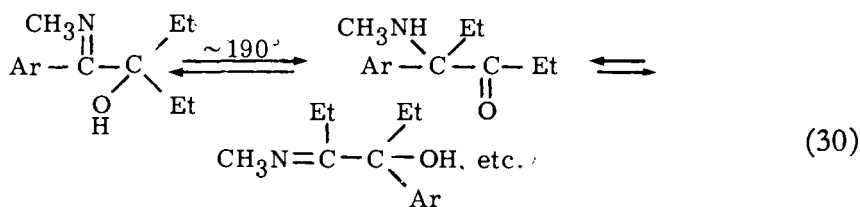
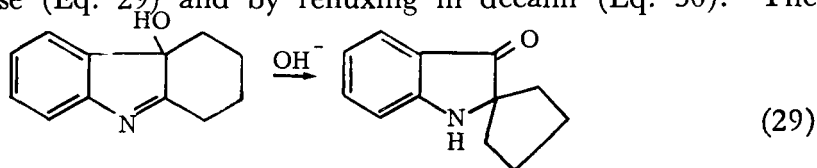


In a closely related reaction, position exchange takes place between the amino group and the carbonyl oxygen ³⁰ (Eq. 28). The principal impor-



tance of the Amadori rearrangement is in sugar chemistry, where it can be used in the synthesis of amino sugars. There seems little doubt that

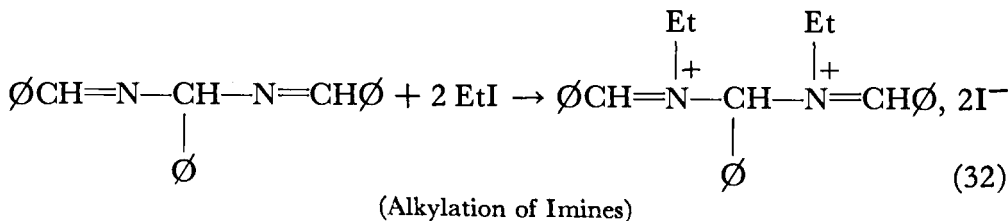
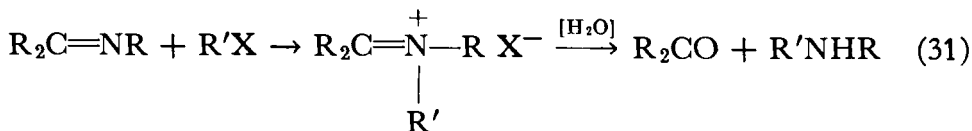
an immonium salt, $RCHOHCR=\overset{+}{N}HR$, is an intermediate,²⁹ but it has not been established whether the next step is simple loss of a proton from the α -carbon, or a concerted shift of a proton from C to N. It has been reported^{29d} that *gem*-diamines undergo the rearrangement under conditions where the imines and the carbinolamines are inert, but the explanation is not clear. When the hydroxyl group is on a tertiary carbon atom, so that hydrogen migration is not possible, rearrangement may occur by migration of an alkyl group.³¹ Such processes have also been brought about by base (Eq. 29) and by refluxing in decalin (Eq. 30). The



(reversible migration of aryl and alkyl groups)

thermally induced reaction has been shown to be reversible, a circumstance that eventually leads to scrambling when the substituents are not all the same.

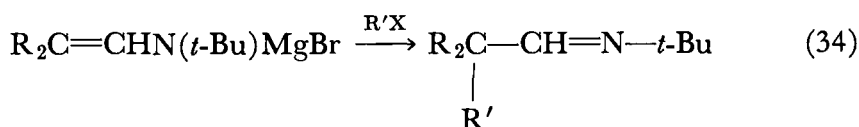
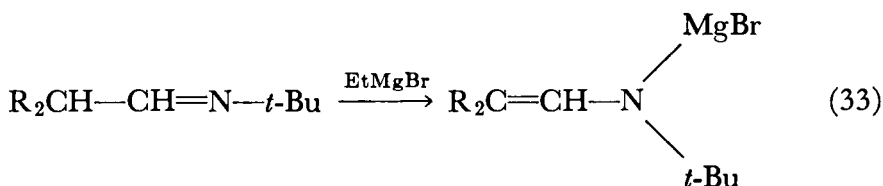
ALKYLATION Imines react with the usual alkylating agents, giving immonium salts¹⁹ (Eqs. 31, 32), but the reaction is slow in keeping with



the low basicity of imines. Many cases are reported in the literature where an immonium salt is formed from an alkyl halide without alkyla-

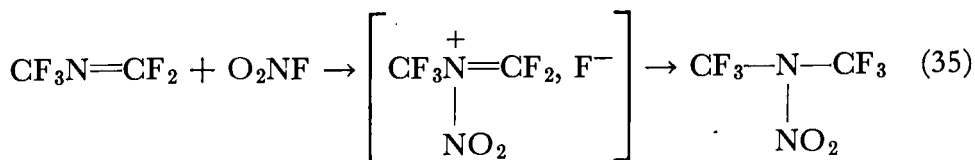
tion, apparently the result of the formation of acid by solvolysis of the alkylating agent.³² Alcohols as well as water can bring about such a result, and in sluggish cases, alkylation of imines can only be accomplished by the strict exclusion of hydroxylic substances. These circumstances have often been overlooked, and inadequately characterized imine hydrohalides are mistakenly recorded as ternary immonium salts. Such mistakes have led to the further erroneous reports that many ternary immonium salts lose an alkyl group (which actually was never there) on mild hydrolysis. An example is *p*-dimethylaminobenzaldehyde anil, whose reaction with methyl iodide was originally reported by Madelung^{33a}; the true methiodide (actually a mixture of isomers) is in fact quite different^{33b} from Madelung's product. When conducted properly, the alkylation of imines with subsequent hydrolysis is a useful preparative method for secondary amines³⁴ (Eq. 31).

Alkylation at an α -carbon can be accomplished if the imine is first converted to a magnesium derivative by reaction with a Grignard reagent³⁵ (Eq. 33); in order to avoid the competing reaction of addition

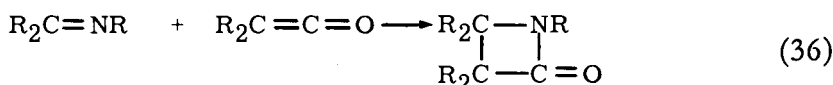


of the Grignard reagent to the imine double bond, the *N*-*t*-butyl imine is used. The α -substitution is apparently direct, rather than indirect through *N*-alkylation and rearrangement, for alkylation with allylic groups occurs without allylic rearrangement.

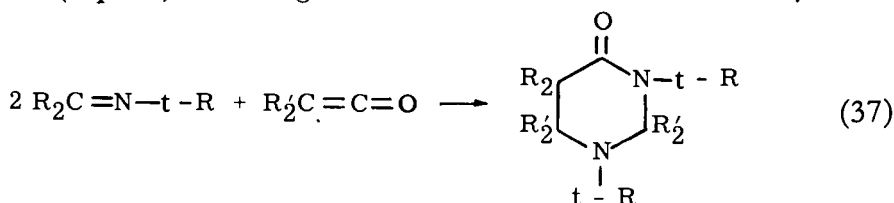
ACYLATION Acylation of imines is not of much importance, and comparatively little attention has been paid to it. Simple acylation would be possible only with imines unsubstituted on the nitrogen, of course, although *N*-alkyl imines could form *N*-acyl immonium salts. A special case of apparent formation and collapse of such a salt is seen in the behavior of a perfluoro imine toward nitril and nitrosyl fluorides, giving a nitramine and a nitrosamine, respectively.³⁶



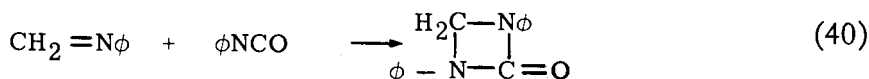
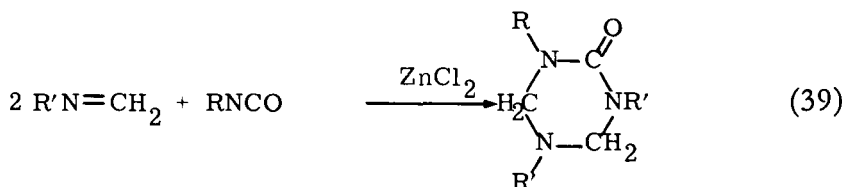
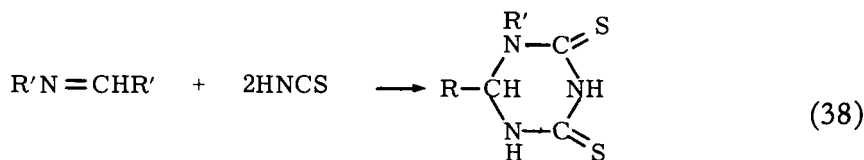
The C—N double bond has not been found to be active as a dienophile in the Diels-Alder reaction, but it will undergo cycloaddition with ketenes ^{36a} (Eq. 36), which may be formally generated *in situ* from an acid



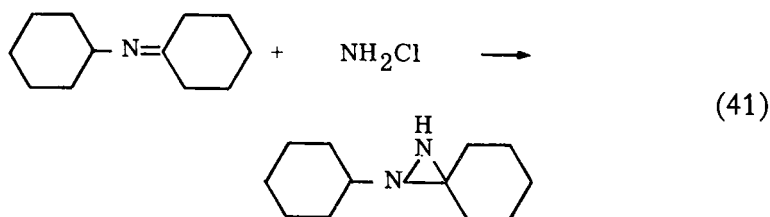
chloride and triethylamine.^{36b} The products are ordinarily β -lactams, but N-*tert*-alkyl imines react with ketene in a 2:1 ratio, giving pyrimidone derivatives (Eq. 37). Analogous reactions ^{36c-e} occur with isocyanates



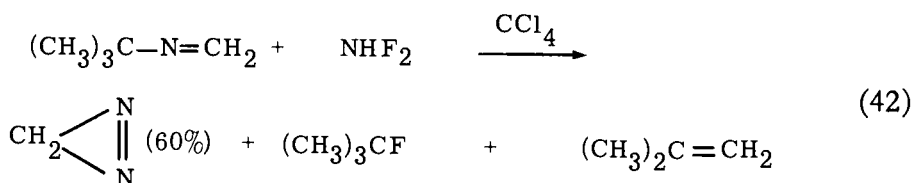
and isothiocyanates, giving triazine derivatives or azetidinones (Eqs. 38–40).



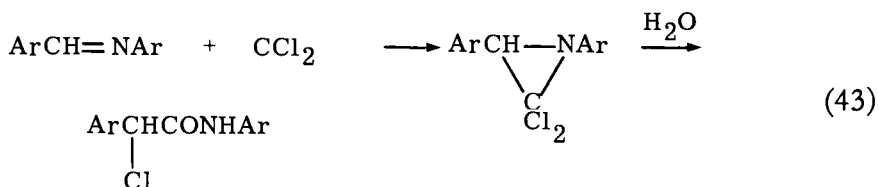
CARBENES AND AZENES Various electron-deficient species add to imines, producing some remarkable structures. Chloramine, a presumed source of NH, converts imines to diaziridines ^{37a} (Eq. 41), in a reaction



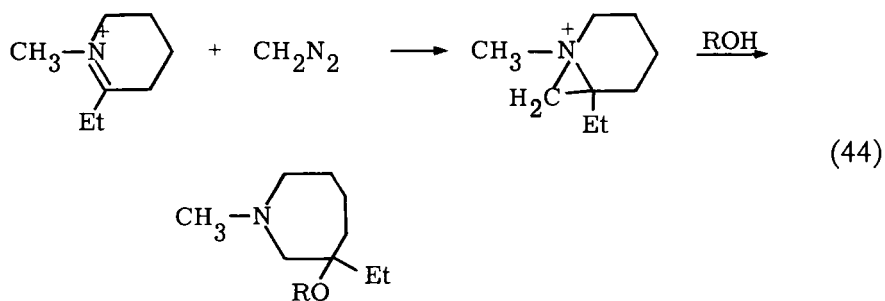
reminiscent of the epoxidation of olefins. Difluoroamine adds to *N*-*t*-butylformaldimine with subsequent elimination of the *tert*-butyl group, forming diazirine ^{37b} (Eq. 42), an isomer of diazomethane. Dichloro-



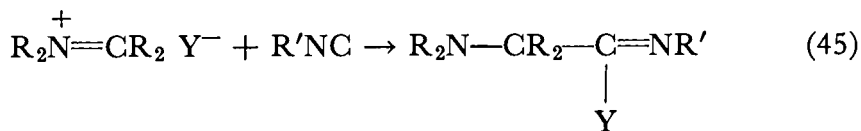
methylene, generated from chloroform and potassium *tert*-butoxide, gives high yields of dichloroaziridines ³⁸ (Eq. 43), which are easily hydrolyzed



with concomitant ring opening to form β -chloro amides. Diazomethane reacts with ternary immonium salts with loss of nitrogen and forms aziridinium salts.³⁹ These reactive products have unusual capabilities for further reactions; in the particular case of those derived from endocyclic immonium salts, for example, alcoholysis leads to ring expansion (Eq. 44).



Isocyanides add to immonium salts to form nonionic substances with incorporation of the original anion ⁴⁰ (Eq. 45), which therefore

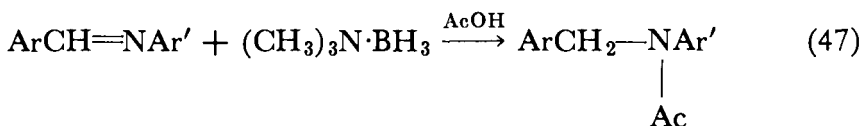


strongly determines the nature of the products. The initial step is probably electrophilic attack by the azomethine carbon atom on the isocyanide carbon; the final products may be the result of tautomerism or cyclization. More is said about these reactions in Chapter 5.

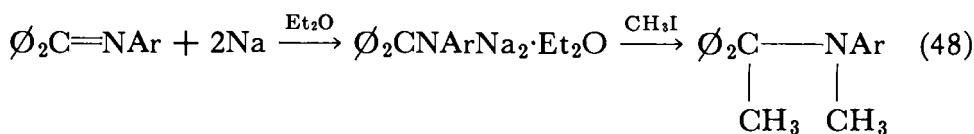
REDUCTION Reduction of imines leads to secondary amines (or to tertiary amines in the case of ternary immonium salts ^{15b}) (Eq. 46) and



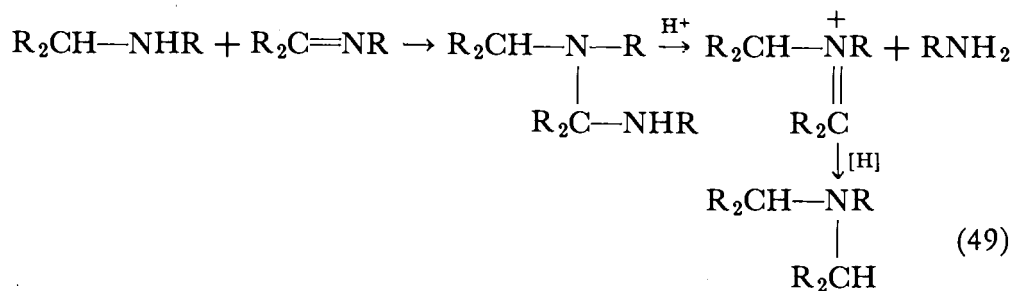
is an important preparative reaction.⁴¹ It has been accomplished by catalytic hydrogenation, by sodium and alcohol, by electrolysis, by aluminum amalgam,⁴² by mercaptans,^{11b} by magnesium plus magnesium iodide,⁴² by sodium borohydride⁴³ or lithium aluminum hydride,⁴⁴ and by formic acid.⁴⁵ The process of reductive alkylation,⁴¹ by which an amine is alkylated by a ketone or aldehyde in the presence of hydrogen and a catalyst, involves reduction of an unisolated imine. Similar remarks apply to the Leuckart reaction⁴⁵ and the closely related Eschweiler-Clarke methylation, in which an amine is heated with an aldehyde or ketone and formic acid or formamide (see Chapter 3). Reductive acylation of imines is brought about by treatment with trimethylamine-borane in acetic acid;



an acetic acid-borane adduct is presumed to be the active agent. Metallic sodium dissolves in solutions of benzophenone anils in ether, giving disodio derivatives of a secondary amine⁴⁶ (Eq. 48).

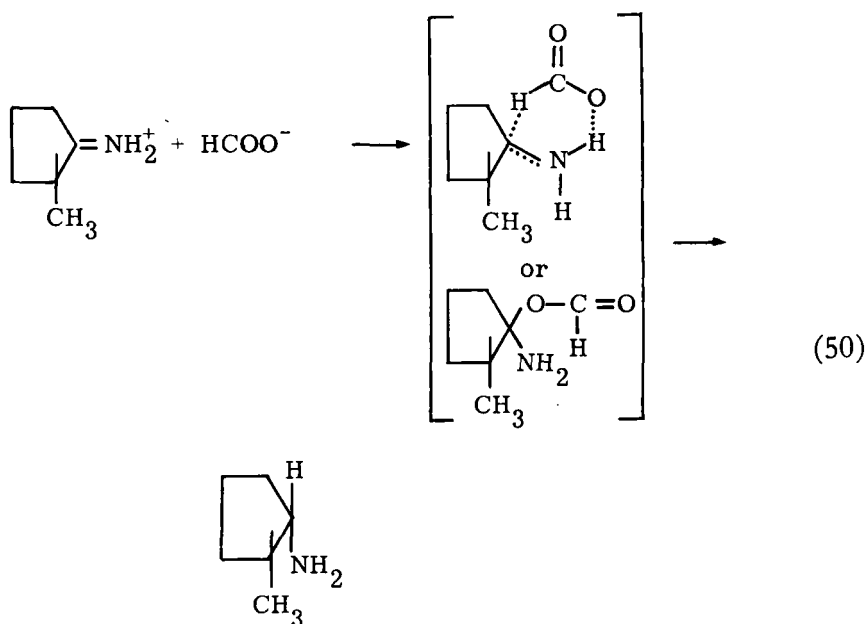


From a preparative standpoint, the reduction of imines is complicated by the fact that amine exchange (transalkylidenation) may occur during the reaction between some of the amine first formed and yet unreduced imine. This produces a new imine (or immonium salt), whose eventual reduction produces a different amine. In this way, tertiary amines may arise from N-substituted imines, and secondary and tertiary amines from imines without a nitrogen substituent (see Chapter 2, "Preparation") (Eq. 49).



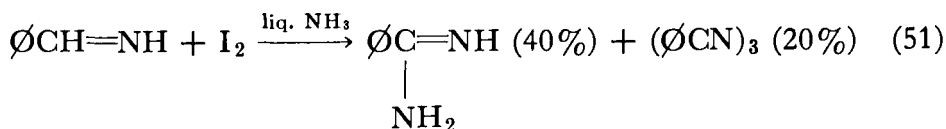
(Formation of Tertiary Amines During Reduction of Imines)

Although all methods of reduction lead to amine (or its acyl derivative), the stereochemical course of the reduction differs with the reducing method. The differences are in general only of consequence with cyclic compounds, where the *cis* and *trans* addition of hydrogen leads to stereochemically distinct products. Dissolving metal reductions generally lead to the more thermodynamically stable product, usually resulting from *trans* addition. Catalytic hydrogenation and formate reductions take place by *cis* addition from the less hindered side, which often forms the thermodynamically less stable product. In the case of the Leuckart reaction, this result probably arises through formation of immonium-formate addition product,⁴⁷ either an ion pair or a carbinolamine ester (Eq. 50).

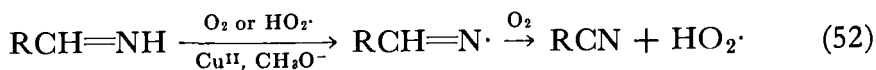


(possible courses of the Leuckart reaction)

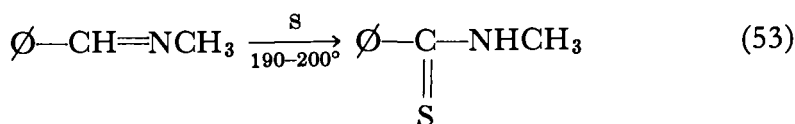
Aldimines are susceptible to oxidation in much the same way as are aldehydes, but because of the ease of hydrolysis, it is not easy to establish the origin of products from oxidations in the presence of water. Benzaldimine can be oxidized by iodine in liquid ammonia,^{5a} however, to produce benzamidine and cyaphenine (trimeric benzonitrile) (Eq. 51). Aldimines



in general can be oxidized smoothly to nitriles by a free-radical chain reaction with oxygen^{48a} (Eq. 52). Sulfur oxidizes benzaldimines to

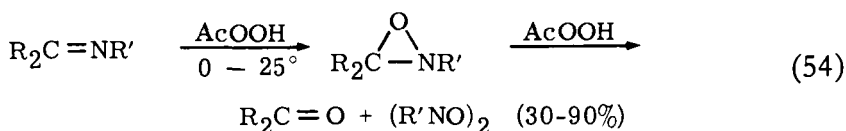


benzthionamides in good yield ^{48b} (Eq. 53). This reaction obviously has

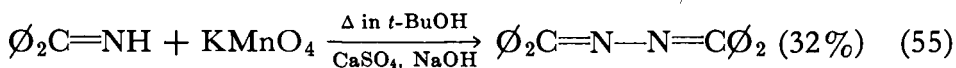


a close relation to the Willgerodt reaction (see Chapter 4, under "Thionamides, Preparation").

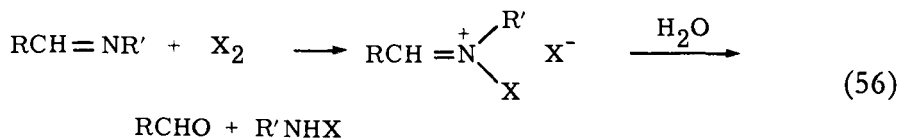
Two types of reaction have been observed with ketimines and peroxidic reagents.^{49a} The simplest process is the addition of an oxygen atom to the double bond, forming an oxazirane, which can be isomerized to a nitron by heating. Complete cleavage of the carbon-nitrogen bond, requiring two molecular equivalents of peroxide, occurs when sufficient oxidizing agent is used; the products are then a ketone and a nitroso dimer (Eq. 54). A yet different type of oxidation is brought about by



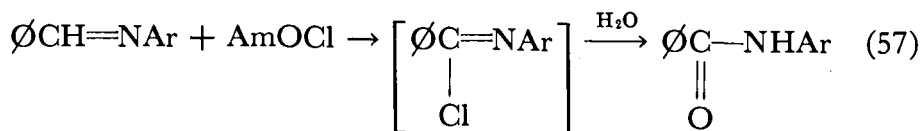
buffered permanganate; some unsubstituted imines are converted to azines by dimerization at the nitrogen atoms ^{49b} (Eq. 55).



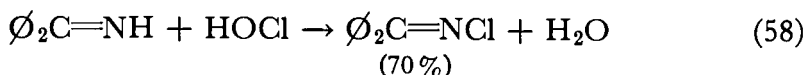
Halogenation ⁵⁰ of imines has been accomplished with free halogen, alkyl hypochlorites, or hypochlorous acid, but the products depend as much on the structure of the imine as on the halogenating agent. With N-substituted aldimines, free halogens form addition products.^{50a,b} They are easily hydrolyzed by water to aldehyde and haloamine, which fact suggests either a vicinal dihalo or an N-halo immonium halide structure (Eq. 56), but the matter is uncertain. Amyl hypochlorite converts



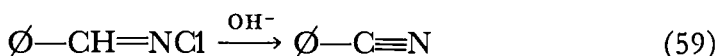
benzaldehyde anils to benzanilides,^{50c} probably through C-halogenation to give an imidoyl chloride, which is subsequently hydrolyzed (Eq. 57); some ring halogenation accompanies the oxidation.



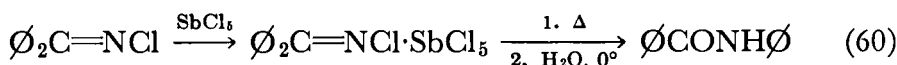
N-Chlorination of benzophenone imines unsubstituted on the nitrogen takes place readily with aqueous hypochlorous acid ^{50d} (Eq. 58). The



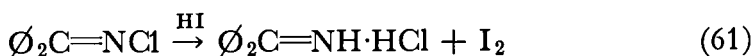
resulting N-halo imines have a chemistry that more closely resembles that of haloamines than imines. N-Chloro aldimines react readily with bases, undergoing elimination with the formation of nitriles ^{51a} (Eq. 59);



the same change can also be brought about by heat alone. As would be expected, acid-strengthening substituents promote the base-catalyzed reaction. N-Chloro ketimines are of principal interest for their role in the early studies of the mechanism of the Beckmann rearrangement. Contrary to early expectations, benzophenone N-chloroimine was found to resist all attempts to induce rearrangement to N-phenylbenzimidoyl chloride, showing that it could not be an intermediate in the Beckmann rearrangement of benzophenone oxime induced by phosphorus pentachloride. In later years, however, rearrangement was successfully accomplished by use of antimony pentachloride ^{51b} (Eq. 60). As with other

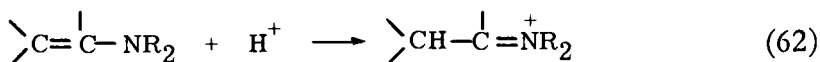


N-halo compounds, N-halo imines are easily reduced by iodide, ^{50d} the halogen being replaced by hydrogen without disturbing the imine double bond (Eq. 61).



B. Enamines ⁵²

The reactions of enamines are distinct from those of imines only in the absence of acid, for the salts that enamines readily form are the result of protonation at the β -carbon atom, and are thus salts of immonium ions (Eq. 62). This has been established ^{4a,c} by comparing the infrared



spectra of enamine salts with neurine derivatives, which contain the struc-

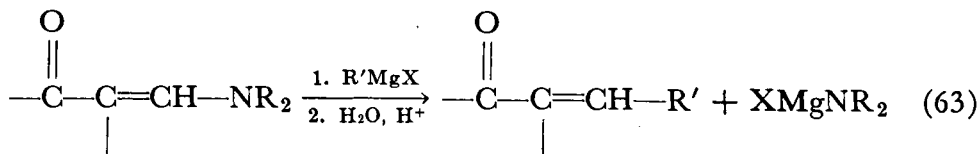
ture $\text{>C}=\overset{+}{\text{C}}-\text{NR}_3$ and do not absorb in the region 1600–1700 cm^{-1} ,

and with compounds of the type $\text{R}_2\text{C}=\overset{+}{\text{N}}\text{R}_2$, which exhibit typical $\text{C}=\text{N}$

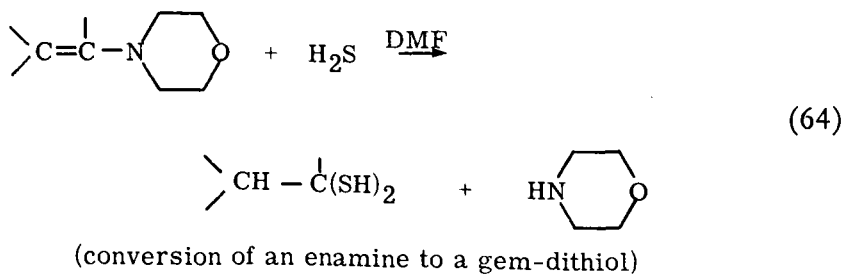
stretching absorption in that frequency region. These observations do not preclude the possibility that for most of the enamine molecules, protonation occurs first at nitrogen, resulting in a rapid equilibrium with an enammonium ion, whereas relatively slow but relatively irreversible protonation at the β -carbon gives the immonium ion. Most of the reactions of imines that take place in the presence of acid, as described in the foregoing section, can therefore be expected to occur with enamines under conditions where even a small extent of salt formation is possible.

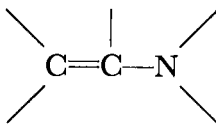
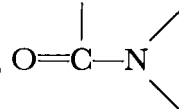
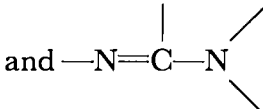
Hydrolysis of enamines of other than endocyclic structure is usually practically instantaneous in aqueous mineral acid, although they are often stable in cold, neutral solution.^{4b} It is generally possible to isolate stable salts because they are prepared in an anhydroxylic medium, although hydrochlorides are often less stable than complex salts, such as chlorostannates⁴ and fluoroborates. Conjugated enamines (derived from α,β -unsaturated ketones) are somewhat less easily hydrolyzed.

NUCLEOPHILES Few reactions of enamines with nucleophiles in the absence of acid are recorded, and enamines, are, in fact, sometimes prepared from immonium salts by treatment with base. N-Vinylphthalimide adds primary or secondary aliphatic amines to produce *gem*-diamine derivatives.^{53a} Grignard reagents apparently do not add to simple enamines unless they are first converted to a salt, such as a perchlorate^{53b}; 3-keto enamines, however, add organometallic reagents, probably in a 1,4 sense, with the net result of replacing the secondary amino group with alkyl or aryl^{53c} (Eq. 63).

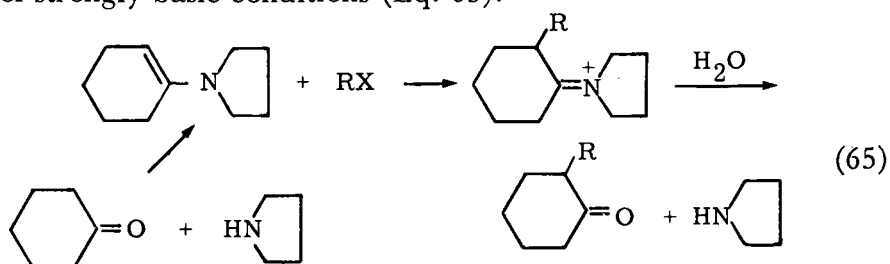


Hydrogen sulfide reacts with enamines in dimethylformamide solution, but the process should probably be properly considered as acid-catalyzed. The first report of this reaction claimed that thioketones were produced, but it was subsequently shown⁵⁴ that the products are in fact *gem*-dithiols, to which the process is a good synthetic route (Eq. 64).



ALKYLATION The enamine triad, , is structurally analogous to the amide and amidine systems,  and , except for the absence of an unshared electron pair on the unsaturated terminal atom. A considerable degree of *pi*-orbital delocalization would be expected, such that the system should properly be treated as a unit, and not as isolated olefin and amine functions. By simple analogy, one would expect alkylation, as well as protonation, to take place on the unsaturated atom, giving an immonium cation.

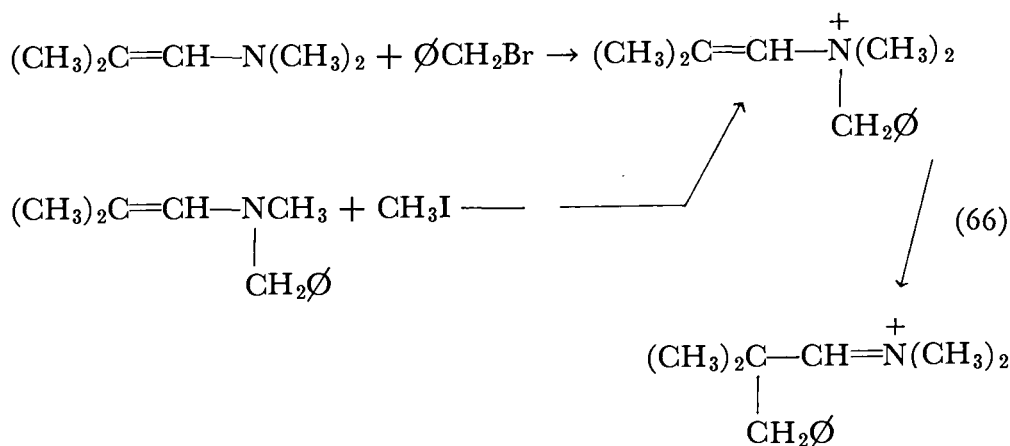
The discovery by Stork and coworkers⁵⁵ in 1954 that enamines can indeed be alkylated at the unsaturated carbon has been responsible for widespread attention to the subject. Although alkylation with simple primary alkyl halides has been accomplished, the yields are not good unless strongly electrophilic alkylating agents, such as allylic and benzylic halides, α -halo ethers, and ketones, etc., are used. When combined with a simple preparative step, and hydrolysis subsequent to alkylation, alkylation of enamines provides a route for the alkylation of ketones and aldehydes that has significant advantages over older methods, which involve the use of strongly basic conditions (Eq. 65).



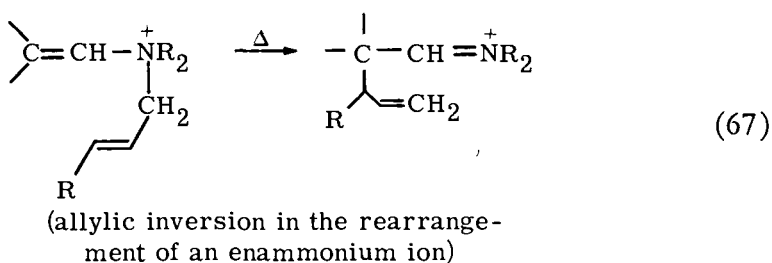
There is a noticeable difference in reactivity among enamines toward alkylation, partly attributable to geometric factors, and partly to electronic.⁵⁵ Pyrrolidine enamines are the most reactive, an expected consequence of the great basicity of pyrrolidine, and they also give the highest ratio of C— to N—alkylation. This has been attributed to the ease with which the nitrogen atom in a five-membered ring can assume a planar, trigonal configuration, as it occurs in the products of C-alkylation. Morpholine enamines, on the other hand, are less reactive, in accord with the much lower basicity of morpholine.

In some cases, and especially with enamines derived from aldehydes, alkylation occurs almost exclusively on the nitrogen, giving enammonium salts,⁵⁶ when simple alkyl halides are used, whereas strongly electrophilic alkylating agents, such as allyl and benzyl halides, give enammonium

salts that easily rearrange to C-alkylated enamines ⁵⁷ (Eq. 66). When an

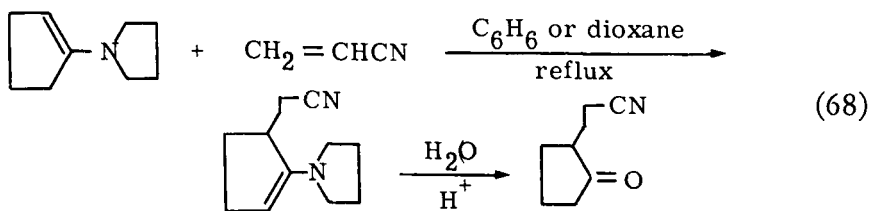


allylic group is involved, structural inversion occurs (Eq. 67), analogous



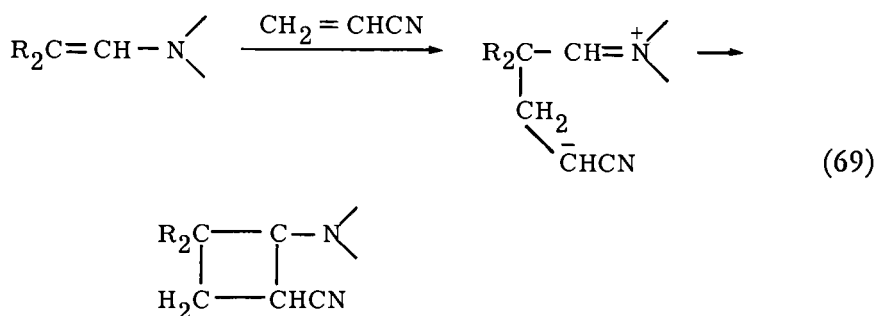
to the Claisen rearrangement and the isomerization of allylic thiocyanates, but it is not yet known whether the migration of benzyl and other groups occurs by ionic dissociation and recombination, or intramolecularly as in the Chapman rearrangement (see Chapter 4). The evidence is not yet sufficient to say whether C-alkylated products are always the result of initial N-alkylation, or whether alkylation at the two sites may in other cases be direct processes competitive with each other.

Alkylation of enamines at carbon can also be accomplished with electrophilic olefins, such as acrylonitrile or methyl vinyl ketone, and in fact, with these reagents N-alkylation is at most a reversible process of little consequence, so that good yields of C-alkylated products can be expected (Eq. 68). The products are themselves enamines, and thus capable of



(C-alkylation of enamines with electrophilic olefins)

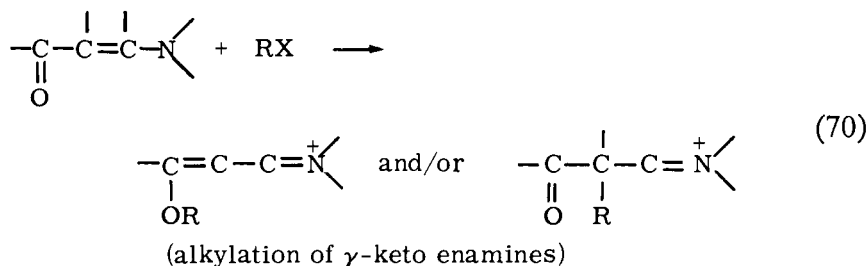
further alkylation, but the introduction of a second group is a much slower process, presumably for steric reasons. These alkylations are accelerated by polar solvents, which fact suggests charge separation in the transition state (Eq. 69). The same intermediate can accommodate



the formation of cyclobutylamine, the result of cycloaddition, observed with enamines derived from α,α -disubstituted aldehydes, in which hydrogen transfer to regenerate an enamine system cannot take place.

C-Arylation of enamines with reactive aryl halides, such as 2,4-dinitrochlorobenzene, has also been observed.⁵³

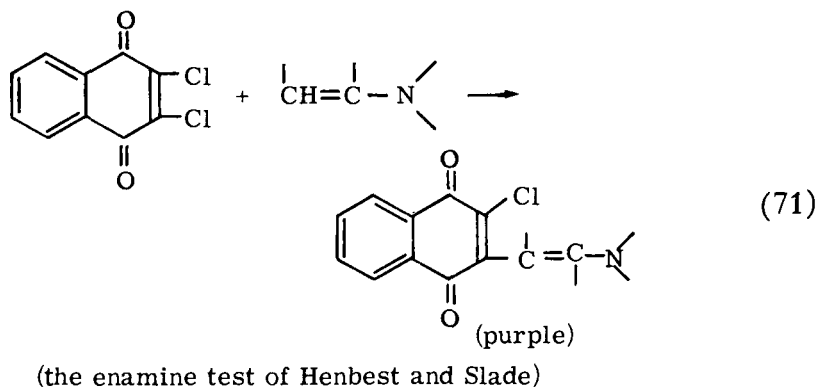
γ -Keto enamines, which contain the structure , are potentially triply ambident nucleophiles, and as such might be expected to receive an alkyl group at N, C, or O. However, they are vinylogous amides, and the entire system from O to N could be encompassed by a delocalized *pi* orbital. Only O- and C-alkylation have been observed,^{4c, 58}



and the absence of N-alkylation can be attributed to the same cause as in simple amides, where alkylation takes place on the doubly bonded atom of a delocalized system. Although studies have so far been only introductory, it has been demonstrated that the site of alkylation is sensitive to both temperature and alkylating agent, and even such a simple change as from methyl iodide to ethyl iodide causes noticeable differences.

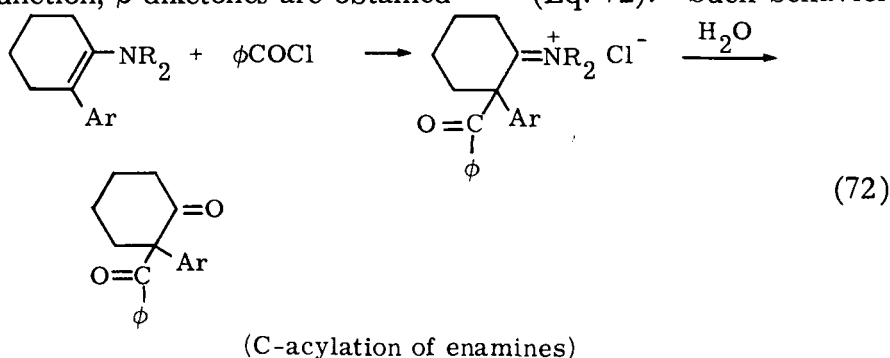
Alkylation of enamines with dichloronaphthoquinone, which occurs at the β -carbon, gives products that are purple, owing to the increased

conjugation (Eq. 71). This has been recommended⁵⁹ as a useful quali-

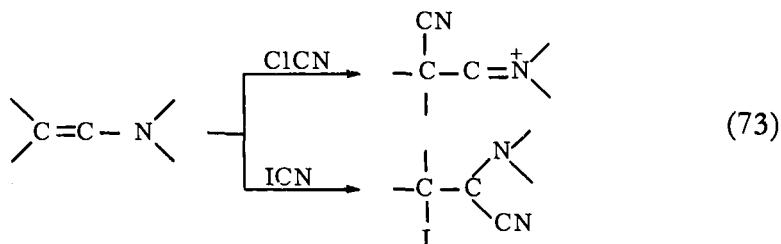


tative test for enamines, not interfered with by the presence of the tautomeric imine.

ACYLATION Treatment of enamines with acylating agents has so far given products derived only from C-acylation⁶⁰; after hydrolysis of the amino function, β -diketones are obtained^{53, 55} (Eq. 72). Such behavior

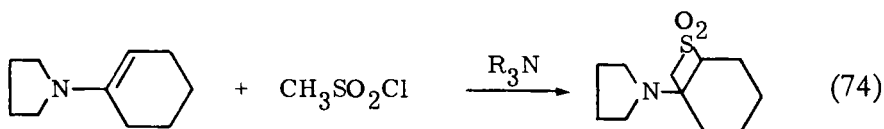


has been observed with acetyl, benzoyl, and *p*-toluenesulfonyl chlorides,⁶⁰ ethyl chloroformate,⁵⁵ anhydrides,⁵⁵ isocyanates and isothiocyanates,^{60c} and cyanogen chloride.^{60d} Cyanogen bromide and iodide function instead as halogenating agents, giving α -amino- β -halo nitriles^{60d} (Eq. 73).



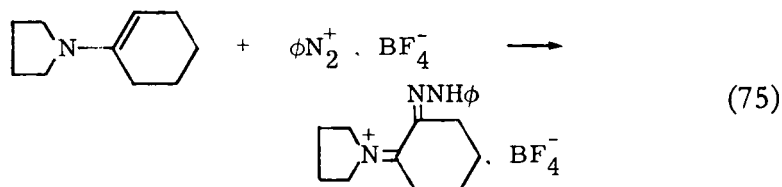
Sulfonyl chlorides bearing an α -hydrogen atom react further, however, perhaps via a sulfene, RCHSO_2 , to form the four-membered thietane ring^{60e,f} (Eq. 74).

A site that is nucleophilic enough to react with alkylating and acylating agents would be expected to be susceptible to other kinds of electrophilic

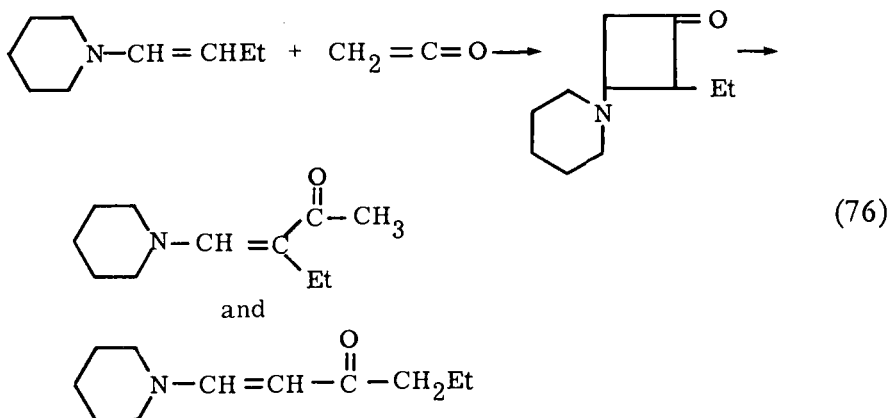


(thietane formation from sulfonyl chlorides and enamines)

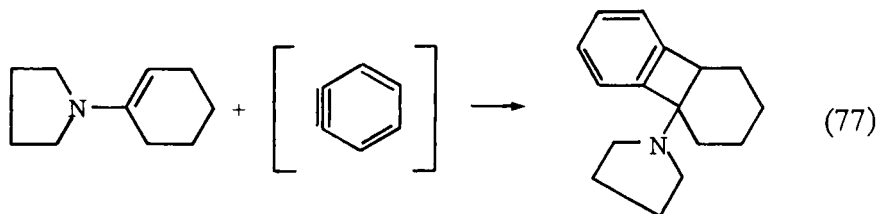
attack as well. This is demonstrated with enamines in the reaction with diazonium salts^{53b, 61}; coupling occurs at the β -carbon, giving β -hydrazono immonium salts (Eq. 75).



CYCLOADDITION Although their electron-rich double bond makes enamines unsuitable as dienophiles, cycloaddition occurs readily between enamines and certain reactive unsaturated compounds.⁶² Ketene, for example, adds to enamines to form cyclobutanones. The cyclobutanone system is unstable if it possesses an enolizable hydrogen, however, and β -aminovinyl ketones, resulting from ring opening, are the products usually isolated^{62b} (Eq. 76).

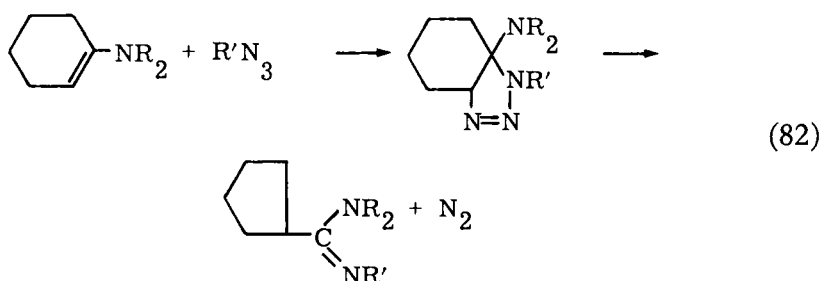


Benzyne, generated from fluorobenzene and butyllithium, forms amino derivatives of benzocyclobutene⁵³ (Eq. 77)



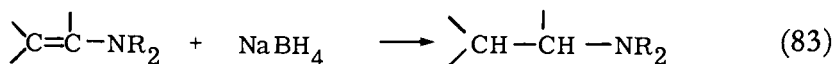
The reactions of enamines with acetylenedicarboxylic ester are of special interest, for they lead to the insertion of two carbons at the original

formation products are actually obtained unless special precautions are taken. Acid usually causes elimination to form a triazole, and heat brings about losses of nitrogen and gives rise to an amidine in good yield (Eq. 82). When the azide is borne by a strongly electrophilic group,



such as 2,4-dinitrophenyl or benzenesulfonyl, the latter reaction may be spontaneous. Rearrangement is obviously involved, consisting of the migration of a hydrogen or alkyl group from the α - to the β -carbon. The over-all effect, taking into account the preparation of the enamine from a ketone, is that of halogenation combined with the Favorskii rearrangement, for amidines can readily be hydrolyzed to carboxylic acids. The mechanism must be different, of course, and probably involves the formation of a transient diazonium inner salt by heterolytic cleavage of the N—N single bond.

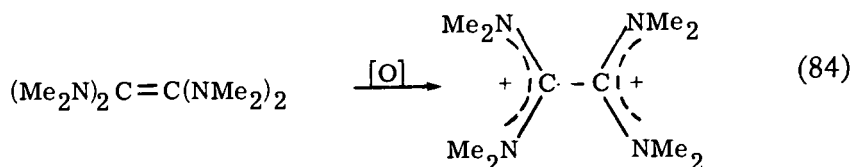
REDUCTION The double bond of enamines is readily reducible by sodium borohydride or lithium aluminum hydride, giving saturated amines⁶⁴ (Eq. 83). Quaternary enammonium salts, however, are appar-



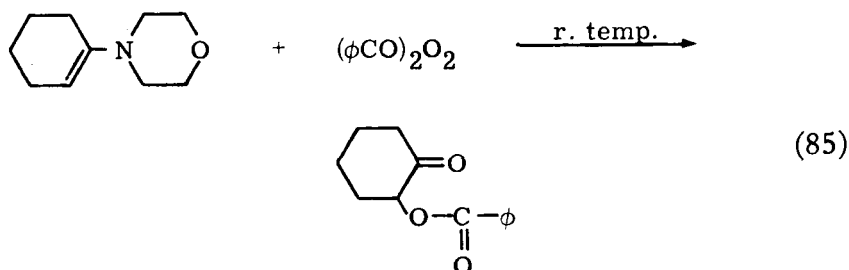
ently more resistant to reduction, and have been reported resistant to catalytic hydrogenation.⁵⁶ Although lithium aluminum hydride successfully attacked an enamine methiodide, the product was found to be a tertiary amine that had lost the original methyl group,⁵⁶ which may very well have been cleaved off prior to reduction of the double bond.

OXIDATION The electron-donating property of the amino group would be expected to enhance the susceptibility of the enamine double bond to oxidation, but little attention appears to have been paid to this aspect of enamine chemistry. However, an unusual extreme is reached in tetrakis-(dimethylamino)ethylene,^{65a} which forms charge-transfer complexes with nitrobenzene, tetracyanoethylene, and other electron-attracting species. Oxidizing agents easily extract two electrons, converting

the enamines to an octamethyloxamidinium salt (Eq. 84). Ordinary

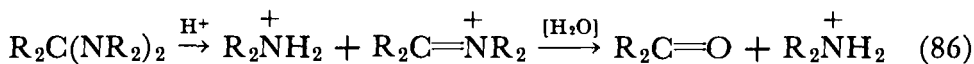


enamines can be oxidized to α -benzoyloxy ketones by benzoyl peroxide, however^{65b} (Eq. 85).



C. *gem*-Diamines

The chemistry of *gem*-diamines, even more than that of enamines, is essentially that of the corresponding imines. Acid easily catalyzes the cleavage of *gem*-diamines into an amine and immonium salt,⁶⁷ and hydrolysis of the latter follows rapidly (Eq. 86).

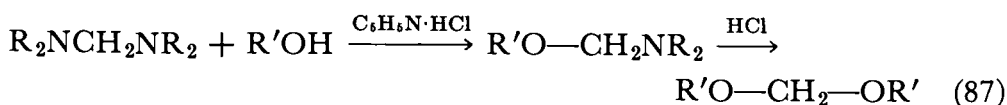


Nevertheless, salts of the more stable *gem*-diamines can be isolated.^{5d} *gem*-Diamines that are derivatives of aniline are likely to undergo ring-forming condensations when treated with acid.

gem-Diamines are quite stable to bases, even in aqueous solution, and many have even been distilled from alkali. One of the stablest *gem*-diamines is hexamethylenetetramine, which can be sublimed above 200°, and resists boiling water. Although the corresponding imine, $\text{CH}_2=\text{NH}$, is not known, its transient existence can be inferred from reactions of hexamethylenetetramine in the presence of acids, even weak ones (but not bases).

gem-Diamines can be alcoholized in the presence of acids, becoming converted to acetals. An excess of alcohol is not needed, and the theoretical quantity in an inert solvent reacts quite well. With a mildly acidic catalyst, such as pyridine hydrochloride, however, the solvolysis

can be halted at the intermediate carbinolamine ether stage ^{5d} (Eq. 87).



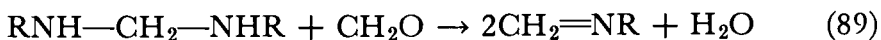
Tertiary *gem*-diamines, $\text{R}_2\text{N}-\text{CR}_2-\text{NR}_2$, are normally stable to heat, and many can be distilled without the use of high vacuum. Secondary *gem*-diamines, $\text{RNH}-\text{CR}_2-\text{NHR}$, on the other hand, are more reactive. Attempted distillation cleaves them into an amine and an imine ⁶⁶ (Eq. 88).



gem-Diamines are known to take part in the Mannich reaction readily,^{68a} but since this reaction is usually carried out in slightly acidic solution, that is not surprising, and may be attributed to cleavage to an immonium salt. Of more significance is the fact that *gem*-diamines will aminoalkylate phenols even in quite strongly basic solution ($\text{pH} \sim 9$), where cleavage is not ordinarily observed. The essential role of the *gem*-diamine species in this reaction has been demonstrated kinetically.^{68b} The rate of aminoalkylation of phenols by morpholine and formaldehyde at constant *pH* increases with the ratio of amine to aldehyde until the ratio 2:1 is reached, after which there is no further change. It should be noted

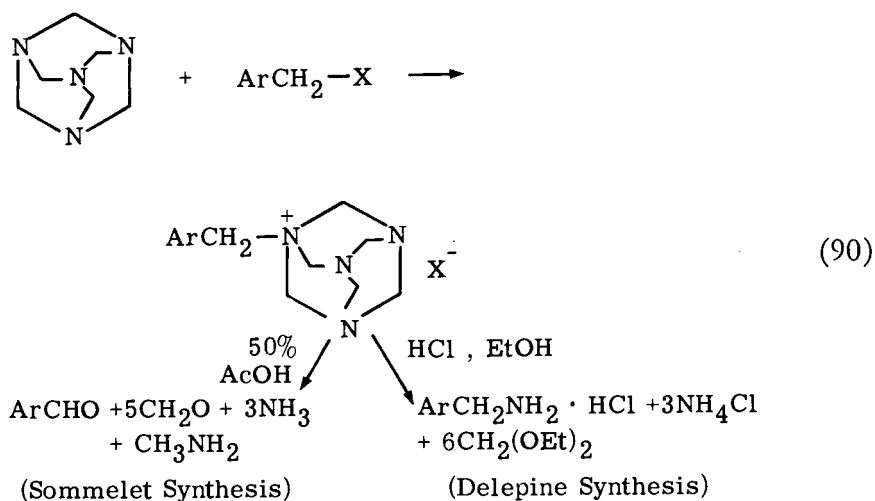
that these facts rule out the immonium ion, $\text{CH}_2=\overset{+}{\text{N}}\text{R}_2$, as a necessary reaction intermediate.

Secondary *gem*-diamines are cleaved by formaldehyde (and would probably be by other aldehydes) to give formaldimines ^{5d} (Eq. 89).

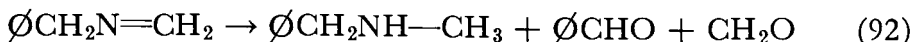
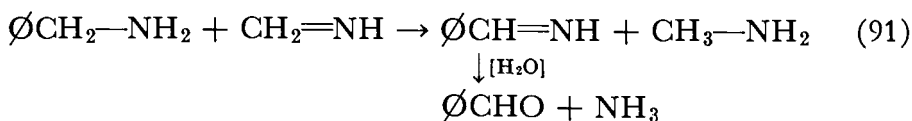


Alkylation of *gem*-diamines is slow, and suggests that the *gem*-diamine structure is less nucleophilic than ordinary amines. The alkylation of hexamethylenetetramine is the most important example, for it is the basis of the Delepine synthesis of primary amines and the Sommelet synthesis of aldehydes ⁶⁹ (Eq. 90). The rate is so slow that it is ordinarily considered that these reactions are limited to the most reactive alkylating agents, the benzylic and allylic halides, although pyridyl-, isoquinolyl-, and indolyl-methylamines have also given good results. Even then, hexamethylenetetramine accepts only one alkyl group, forming what are called alkylhexaminium salts.

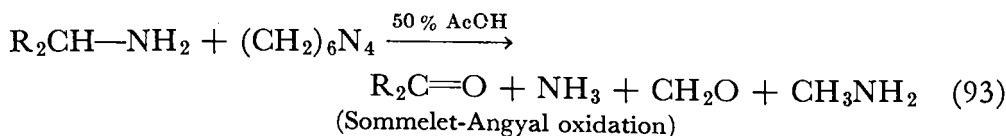
The reactions that follow the formation of the hexaminium salt depend on the treatment. The use of alcoholysis to remove formaldehyde and its derivatives as relatively inert formaldehyde acetal restricts the process



to simple solvolysis, and a primary amine is formed in good yield. In aqueous acid, however, oxidation-reduction comes into play, and the original alkylating agent appears as an aldehyde, often in good yield. The exact nature of the oxidation step has not been fully established, but the evidence is against a simple prototropic shift as the means. Hydrogen transfer between the primary amine and the hypothetical formaldimine, perhaps through a four-center transition state, is the most acceptable explanation. In support of this are such observations as that N-benzylformaldimine when exposed to the reaction conditions is converted largely to methylbenzylamine and benzaldehyde, rather than to the methylamine and benzaldehyde that prototropic shift would demand (Eqs. 91, 92).



A further application of these processes is the use of hexamethylenetetramine in acetic acid solution as a mild and specific oxidizing agent for converting amines to aldehydes or ketones ⁷⁰ (Eq. 93).



gem-Diamines may also be reduced by more conventional means, although many such reactions give only the products to be expected of reduction of the corresponding imine. Alkaline reduction, such as by

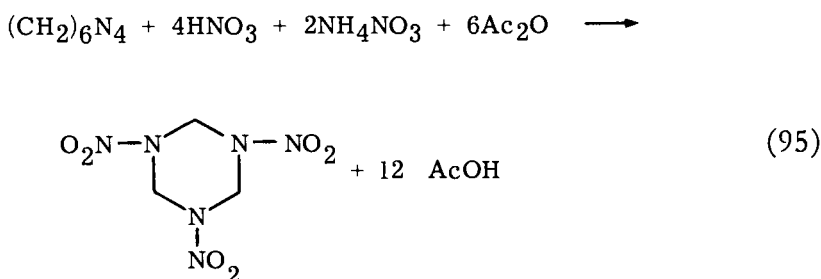
zinc and alkali, gives both tertiary and secondary amines,⁷¹ (Eq. 94) how-



ever, and has provided fundamental evidence concerning the structure of such *gem*-diamines as the trimeric imines.

Oxidation of trimeric imines (hexahydrotriazines) with peroxyacetic acid gives the same oxaziranes as are obtained from the monomeric imines,^{49a} the weak acid being sufficient to bring about depolymerization. Oxidation of *gem*-diamines under strictly alkaline conditions does not appear to have been reported.

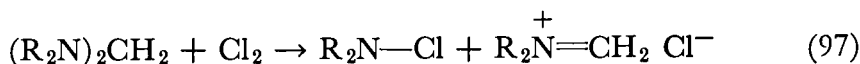
The nitration of hexamethylenetetramine is a reaction of historical importance, for it leads to trimethylenetrinitramine,⁷² known as the explosive cyclonite or RDX, which played a decisive role in antisubmarine warfare in World War II. The process is a nitrolysis and is nonoxidative, and if it is carried out in the presence of ammonium nitrate and acetic anhydride, two moles of product can be obtained from each mole of hexamethylenetetramine.



Acid chlorides in general cleave one amino group from *gem*-diamines as an amide, leaving an immonium chloride⁷³ (Eq. 96). This reaction



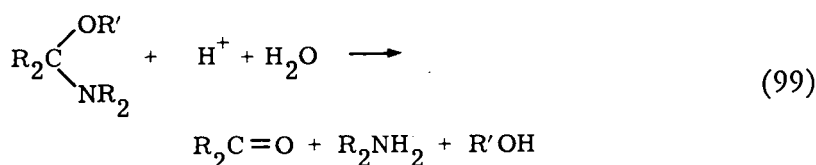
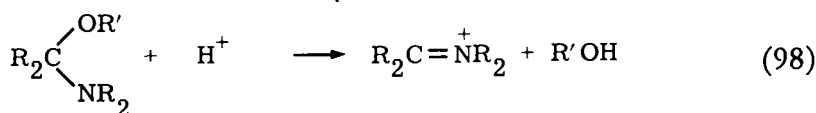
is a useful preparative method for immonium salts, for the yields and purity are high. The behavior of *gem*-diamines toward chlorine is analogous; a chloramine and an immonium chloride are formed⁶⁷ (Eq. 97).



D. Carbinolamines and Derivatives

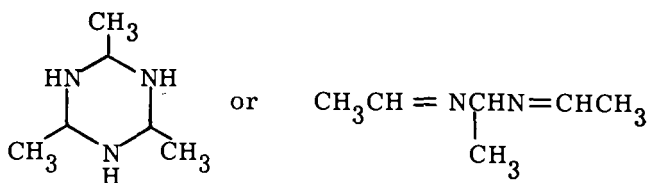
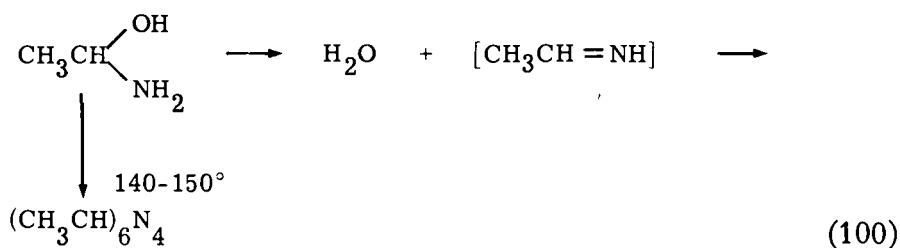
As with *gem*-diamines, the reactions of carbinolamines in the presence of an acid are essentially those of the immonium salts derived from them.^{5d} Hydrolysis of carbinolamines and their ethers is generally rapid in aqueous acid,^{74a} and attempts to prepare salts lead instead to elimination or

hydrolysis products ^{74b} (Eqs. 98, 99). The dissociation of quaternary



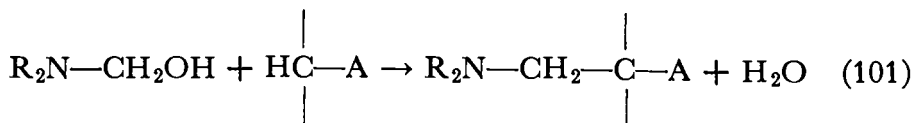
carbinolamines, such as formochlorine, $\text{HOCH}_2\text{N}^+(\text{CH}_3)_3$, does not require acid catalysis.⁷⁵

Heating carbinolamines containing —OH or —NH causes rapid dissociation, usually followed by other reactions. α -Aminoethanol (acetaldehyde ammonia) readily loses water, for example, but the resulting acetaldimine polymerizes ^{5a} either to the cyclic trimer or to triethylidenetriamine (hydracetamide) (Eq. 100). When heated strongly, it forms



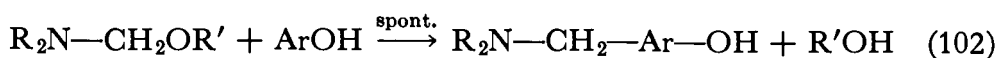
hexaethylidenetetramine, the hexamethyl derivative of hexamethyltetramine. The most general path for carbinolamine decomposition seems to be that leading to cyclic trimers.

Carbinolamines are active aminomethylating agents, and can be used in the Mannich reaction with active hydrogen compounds ⁷⁶ (Eq. 101),



although there seems to be no synthetic advantage to such use. The reaction of phenols, naphthols, and naphthylamines with carbinolamine

ethers (Eq. 102) has been claimed to be especially easy, and to proceed

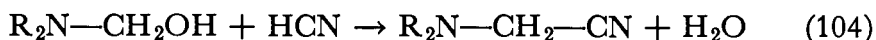


without added acid even at room temperature, sometimes exothermically.⁷⁷

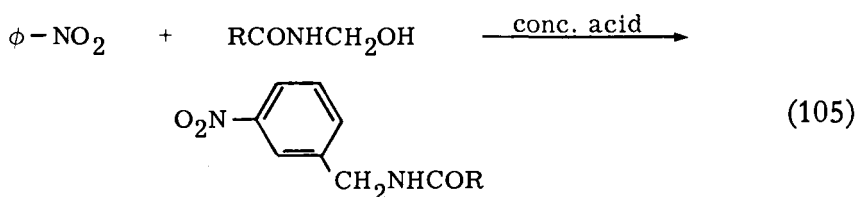
The reaction with primary or secondary amines is a good source of *gem*-diamines (Eq. 103). A similar reaction with hydrogen cyanide,



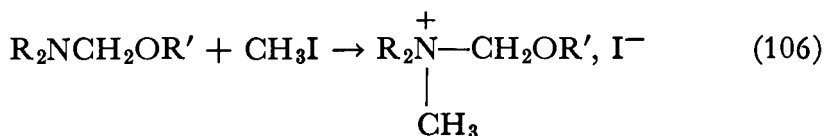
leading to α -amino nitriles, plays a role in the Strecker synthesis^{15d} (Eq. 104).



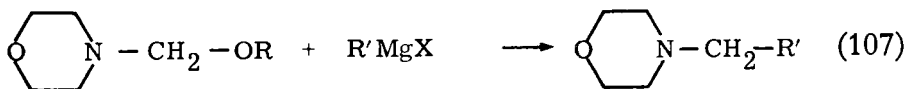
Amidomethylation of aromatic rings can be accomplished with N-methylolamides, even when the ring is not activated, by use of concentrated acid⁷⁸ (Eq. 105). This process is sometimes referred to as Einhorn amidomethylation.



The successful alkylation of carbinolamine ethers has been reported⁷⁹ (Eq. 106).



The reaction of Grignard reagents with some carbinolamine ethers has been found to cleave the C—O bond in preference to the C—N bond, giving tertiary amines^{74b} (Eq. 107).

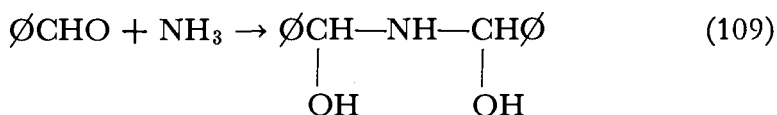
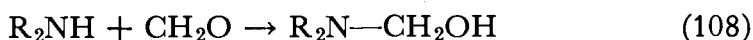


PREPARATION

The preparative reactions that lead to imines are quite varied, and the proper choice is usually dictated by the type of substitution desired. The selection of methods for *gem*-diamines, carbinolamines, and enamines is much more limited, and consists almost entirely of reactions leading

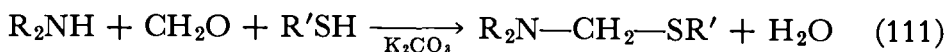
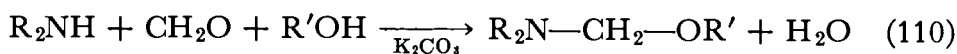
from aldehydes or ketones, or of interconversions. The various reactions that lead from carbonyl compounds to ammonia derivatives⁸⁰ will therefore be taken up first.

The first step in the reaction between carbonyl compounds and ammonia or amines must be the formation of a carbinolamine, but only exceptionally is it possible to stop the reaction at this stage.^{5d} So easily are carbinolamines dehydrated that the conditions required to initiate reaction between amines and ketones are usually more than sufficient to decompose the intermediate carbinolamine; as a result, it is only the most reactive carbonyl compounds, generally only aldehydes, that give isolable carbinolamines⁸¹ (Eq. 108). Among ketones, even acetone will



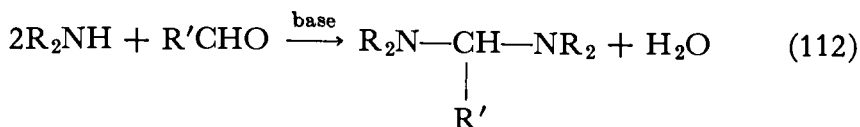
not give a simple carbinolamine with ammonia.⁸² Carbinolamides are somewhat easier to isolate. It is a general rule that carbinolamines must be prepared near room temperature and under alkaline conditions, but without the presence of excess amine, which could lead to *gem*-diamine.

When the reaction between an amine and an aldehyde is carried out in alcohol solution, the carbinolamine ether is formed in substantial amounts in equilibrium with the other possible products^{74b, 77, 79, 83} (Eq. 110). With mercaptans, carbinolamine thioethers are formed (Eq. 111).



These preparations usually occur well only with formaldehyde, but the formation of cyclic carbinolamine ethers (oxazolidines) from β -hydroxy amines not unexpectedly goes much more readily.

gem-Diamines can be prepared from an excess of amine and an aldehyde, especially formaldehyde, in a basic environment^{5d, 74b} (Eq. 112).



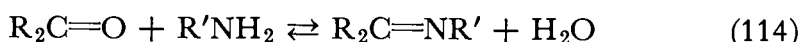
With a mixture of an amine and an amide, a monoacyl *gem*-diamine can be prepared. The formation of *gem*-diamides from amides and formalde-

hyde requires acid, however (Eq. 113), for without it, the reaction stops



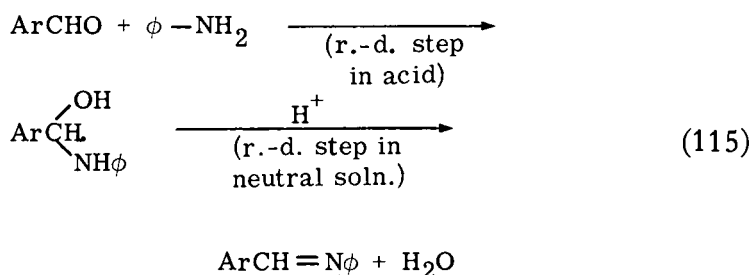
at the carbinolamine stage.

Heating primary amines with aldehydes and ketones produces imines ^{80, 84} (Eq. 114). The reaction is reversible and reaches equilibrium



noticeably short of completion, ^{84e-g} necessitating some method of removing the water produced if an imine is to be prepared in good yield. Azeotropic distillation with benzene is commonly used, preferably with a Dean-Stark trap, which allows the benzene layer, containing much of the volatilized amine, to return to the reaction mixture.

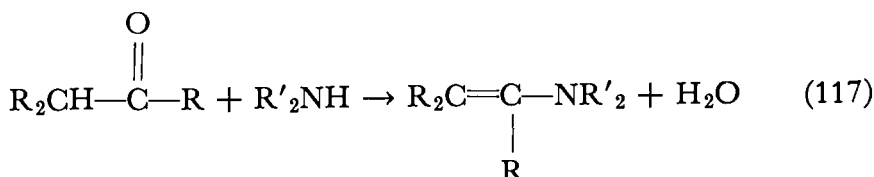
The formation of imines is subject to general acid catalysis, but a catalyst is not customary when aliphatic amines are used. Increasing acid concentration drives the equilibrium away from imine formation, however, since amines are in general more strongly basic than the corresponding imine. The equilibrium constant for the formation of *p*-chlorobenzaldehyde anil, for example, is 4.6 at pH 6.34, but the equilibrium constant for the formation of the corresponding immonium cation from the aldehyde and anilinium ion is only 0.80. ^{84f} The rate-determining step in these reactions is apparently dehydration of the intermediate carbinolamine in neutral solution, changing over to formation of the carbinolamine as acidity increases (Eq. 115). The result is a maximum



rate at about pH 4, analogous to oxime and semicarbazone formation. The reaction of benzophenones, which is relatively sluggish, with anilines is best carried out in the presence of fairly strong acid, ^{84g} such as zinc chloride or 40% hydrobromic acid (Eq. 116).

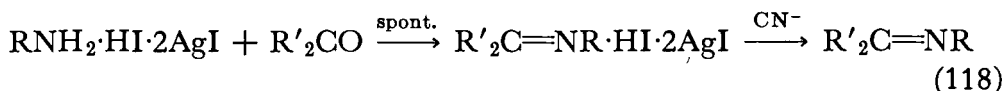


Heating secondary amines with aldehydes or ketones bearing at least one α -hydrogen produces enamines ⁵⁵ (Eq. 117). The reaction can be carried out by refluxing in benzene, ^{4, 64a} using a water trap, with or

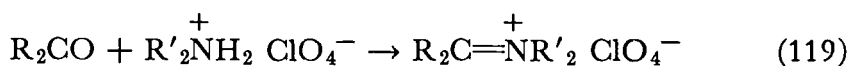


without a small amount of toluenesulfonic acid as catalyst, or near room temperature in the presence of calcium chloride⁸⁵ or potassium carbonate⁴ to take up the water (most suitable with aldehydes). It is of special interest that unsymmetrical cyclic ketones, which could give rise to a pair of structurally isomeric enamines, actually give that one having the double bond to the *less* substituted carbon, the opposite of the expectation on the basis of the relative stability of isomeric enols. It has been proposed⁵⁵ that the cause is steric.

The use of dry salts of amines for reaction with ketones or aldehydes is often advantageous; the reactions are not uncommonly spontaneous and exothermic.⁸⁶ Amine hydroiodide-silver iodide adducts have been used to prepare certain imines that are too labile for satisfactory preparation by other methods, for example^{86a} (Eq. 118). The imine complex



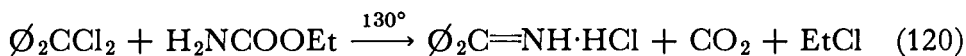
that is initially formed must be broken up by an alkali cyanide to release the free imine. Secondary ammonium perchlorates react with many aldehydes and ketones spontaneously or with slight warming to give ternary immonium salts in high yield^{86b} (Eq. 119).



Interconversions among imines, enamines, *gem*-diamines, and carbinolamines are often easy, and sometimes of use in synthesis. The reaction of carbinolamines with a secondary amine leads to *gem*-diamines,^{5d} for example, and can be used to prepare unsymmetrical products, $\text{R}_2\text{N}-\text{CH}_2-\text{NR}'_2$. The reverse type of reaction, the conversion of a *gem*-diamine to a carbinolamine ether, can be accomplished by treating with an alcohol in the presence of pyridine hydrochloride.^{5d} Distillation of *gem*-diamines is often sufficient to cleave them to enamines⁵⁵ if there is a β -hydrogen on the alkylidene group. The easy dehydration of carbinolamines to imines has already been mentioned; carbinolamine ethers are also easily converted to imines, acid being the required agent.⁷³ The cleavage of secondary *gem*-diamines to two molecules of imine by formaldehyde^{5d} has also been mentioned. The isomerization of secondary enamines to imines occurs readily, but is not prepara-

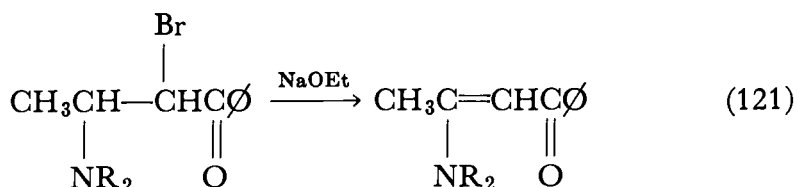
tively significant except insofar as it may be an intermediate stage in other preparative methods. The preparation of ternary immonium salts by protonation of enamines is a valuable method, however.⁴ The preparation of *gem*-diamines by the addition of amines to imines,¹³ of carbinolamines by the addition of water to imines,⁸⁷ of carbinolamine ethers by the addition of alcohols to imines,^{9, 15b} and of *gem*-diamines by the addition of amines to enamines^{53a} has been mentioned under "Reactions." Finally, it should be pointed out that the polymerization of imines usually produces substances that are *gem*-diamines.

When the direct reaction of carbonyl compounds with amines is unsatisfactory because of slowness or reversibility, it is sometimes of advantage to use *gem*-dihalides,^{3a, 87a,b} which may, in fact, be satisfactorily prepared from the carbonyl compounds in many cases, especially from benzophenones. Benzophenone imine, for example, is conveniently prepared by heating benzhydrylidene dichloride with urethan^{50, 88a} (Eq. 120) or

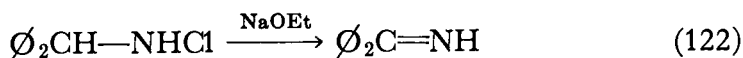


the dibromide with ammonia^{88b}; methylenedipiperidine has been prepared from piperidine and methylene iodide.^{5d} Acetals have also been used with advantage.^{88c}

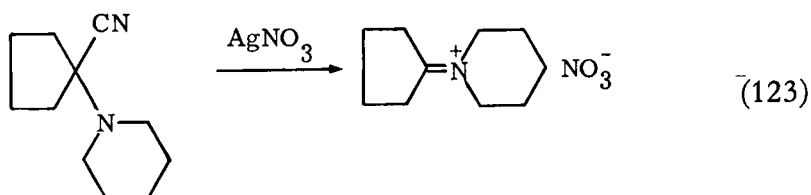
Both imines and enamines can be prepared by dehydrohalogenation reactions. Tertiary amines bearing a β -halogen can be dehydrohalogenated to enamines when other structural features assist⁸⁹ (Eq. 121).



Chloramines can also be converted to imines by strong base⁹⁰ (Eq. 122).

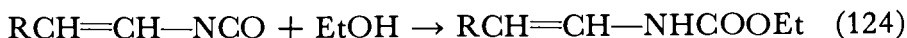


Closely related is removal of the cyanide ion from α -amino nitriles by silver nitrate,⁸ which gives the corresponding immonium salt (Eq. 123).

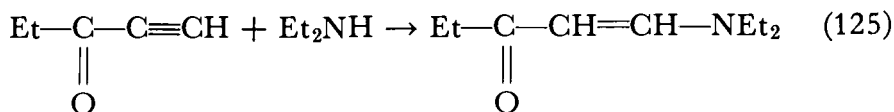


Certain addition reactions give rise to imines in preparatively useful yield. The oldest example is probably the addition of alcohols to vinyl

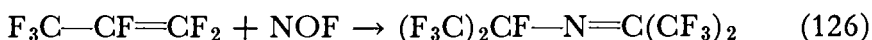
isocyanates (obtained from the Curtius rearrangement of α,β -unsaturated acyl azides) ⁹ (Eq. 124). The addition of acetylenic ketones to second-



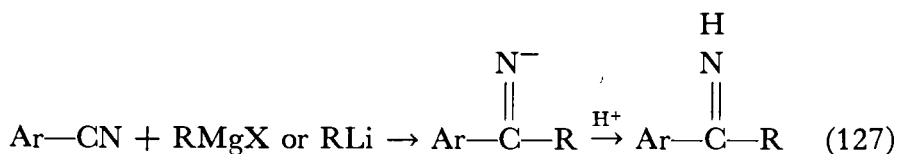
ary amines produces γ -keto enamines ^{4c} (Eq. 125). A special reaction



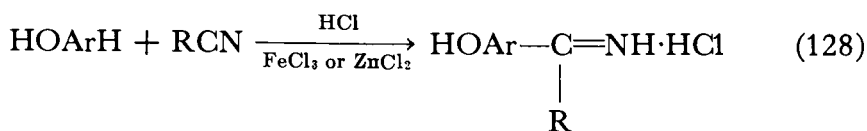
applicable only in the field of perfluoro compounds is the free-radical addition of nitrosyl fluoride to perfluoropropene, which ultimately produces perfluoroacetone perfluoroisopropylimine ^{3b} (Eq. 126).



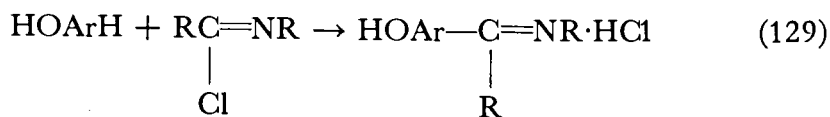
Addition reactions of nitriles are of wide preparative use for imines. The reaction with organometallic compounds, well known as a synthesis of ketones (see Chapter 5), first produces ketimine salts, which can be converted to free ketimines if they are acidified carefully ^{7b, 91} (Eq. 127).



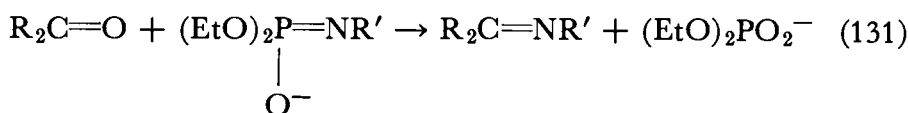
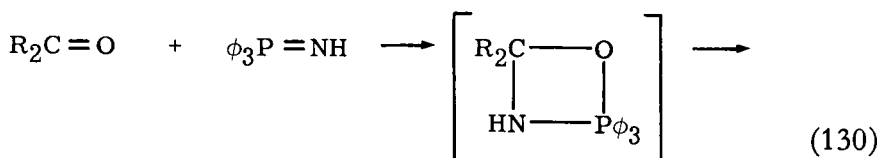
The Hoesch synthesis, ⁹² by which ketones are produced from nitriles and reactive benzene derivatives under Friedel-Crafts conditions, also gives rise to imines (as their hydrochlorides) as the primary products (Eq. 128). N-Substituted imines can be prepared by the similar reaction



of imidoyl chlorides (Eq. 129).



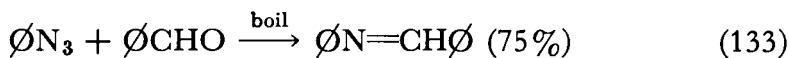
Recent years have seen the introduction of iminophosphorus compounds as reagents for the conversion of carbonyl compounds to imines ⁹³ (Eqs. 130, 131). The primary step is apparently cycloaddition to form a phosphoxazetidine, which easily breaks up into an imine and the oxo isotere of the iminophosphorus compound. The reactions are effective preparative methods.



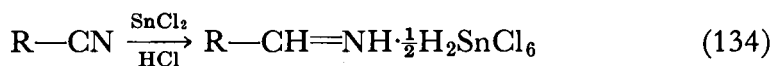
Another preparative reaction that apparently involves ring formation (thiatriazoline) and cleavage is that between azides and thioketones^{94a} (Eq. 132). Superficially the same sort of reaction has been accomplished



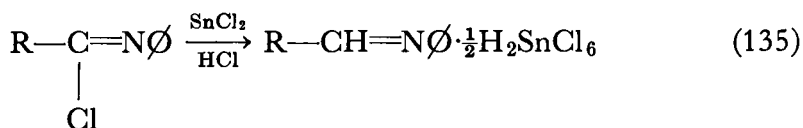
by boiling solutions of phenyl azide in benzaldehyde or cyclohexanone,^{94b} but a reducing agent (presumably excess aldehyde or ketone) is obviously required (Eq. 133).



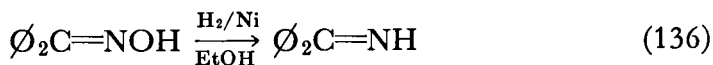
There are several reductive reactions that lead to imines or enamines. The simplest is the addition of two hydrogen atoms to nitriles to produce aldimines. This is accomplished smoothly by anhydrous stannous chloride and hydrogen chloride,⁹⁵ and is known as the Stephen reduction (Eq. 134). The products are obtained as the chlorostannate salt, but



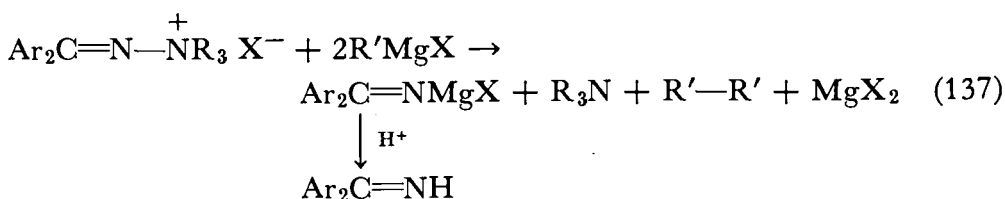
the principal use of the reaction is the preparation of aldehydes by subsequent hydrolysis. A closely related reaction is the Sonn-Müller reduction,⁹⁶ in which imidoyl chlorides, prepared by the action of phosphorus pentachloride on anilides, are converted into aldehyde anils (Eq. 135).



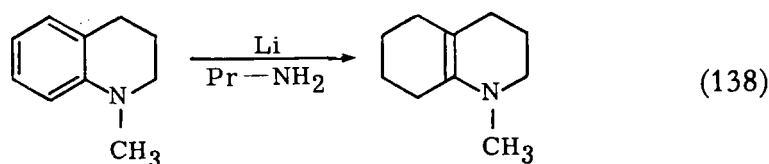
The reduction of oximes is not regarded as a general synthesis of imines, for it is not easily stopped short of complete reduction to an amine, but reduction to an imine has been accomplished in some instances⁹⁷ (Eq. 136). Similar remarks apply to the reduction of hydrazones; good yields



of benzophenone imines have been obtained from quaternary hydrazones by reduction with organometallic reagents ⁹⁸ (Eq. 137).

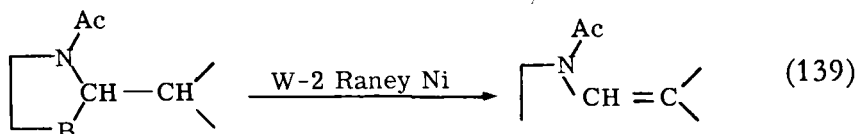


Enamines of cyclic structure are conveniently synthesized by the reduction of aromatic compounds with lithium and an alkylamine ⁵⁶ (Eq. 138).

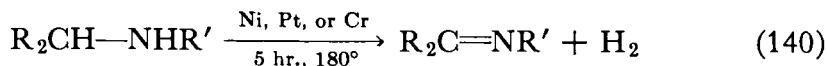


It appears that this means of reduction of aromatic amines in general produces enamines as the primary product.

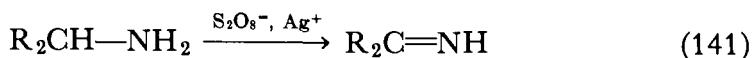
Reductive desulfurization of N-acyl thiazolidines with Raney nickel is a general method for preparing N-alkyl enamides ⁹⁹ (Eq. 139).



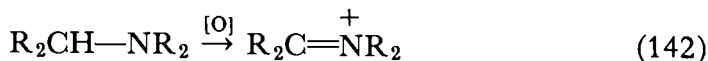
Oxidation of primary, secondary, or tertiary amines can be carried out so as to give useful yields of imines or enamines. The simplest method is catalytic dehydrogenation,¹⁰⁰ a reaction that is, of course reversible (Eq. 140). Various chemical oxidizing agents have been used, such as peroxy-



disulfate in the presence of silver ion,¹⁰¹ nitrosyl compounds,¹⁰² mercuric acetate,¹⁰³ etc.¹⁰⁴ (Eq. 141). Most of these oxidations take place in an

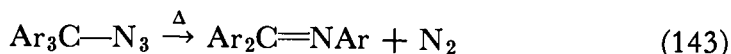


acidic environment, and thus produce immonium salts; those derived from tertiary amines (Eq. 142) readily go over to enamines on neutralization.



There are several rearrangement reactions that lead to imines, although none of them can at present be regarded as preparatively impor-

tant. The thermal rearrangement of triarylmethyl azides ¹⁰⁵ (Eq. 143),



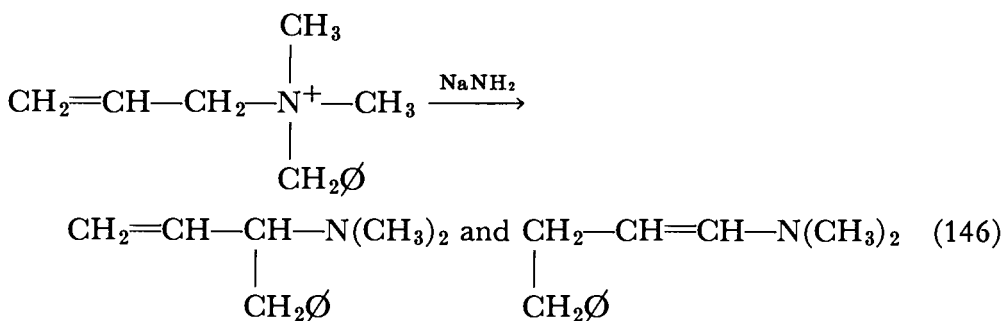
the base-induced rearrangement of triarylmethylchloramines (see Chapter 4) (Eq. 144), and the rearrangement of triarylmethylhydroxylamines ¹⁰⁶



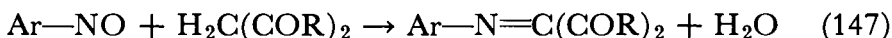
by phosphorus pentachloride (Eq. 145) all yield benzophenone anils.



The Stevens rearrangement of allyl quaternary ammonium compounds has recently been shown ¹⁰⁷ to yield enamines by migration of a benzyl group (Eq. 146).

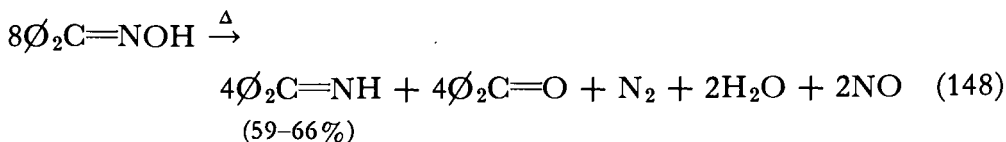


An important reaction for preparing certain types of imines starts from nitroso compounds, which condense with active methylene compounds in much the same way as do aldehydes and ketones ¹⁰⁸ (Eq. 147). The



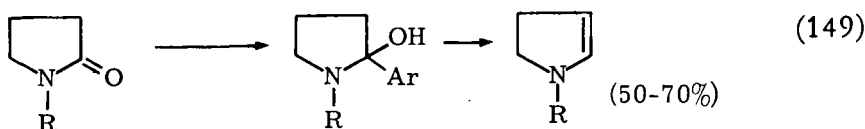
usefulness of this method is limited by the availability of nitroso compounds essentially to the preparation of anils, particularly *p*-dimethylamino anils.

The disproportionation of oximes brought about by pyrolysis gives surprisingly good yields of imines in special instances,¹⁰⁹ such as benzophenone oxime, where the structure limits the possibilities for competing reactions (Eq. 148).



The synthesis of enamines from amides is in principle possible by addition of a Grignard reagent followed by dehydration. Although such a procedure appears to have no value with open-chain amides, owing

to dominating side reactions, it works well with lactams, giving endocyclic enamines ¹¹⁰ (Eq. 149).



OTHER IMINES

Phosphine imines, $R_3P=NR'$, and sulfinimes, $R_2S(O)=NH$, are reasonably well-known classes of substances that bear an obvious relationship to aldimines and ketimines. Their chemistry has been much less extensively investigated, however. Except insofar as they are involved in the preparation or reaction of other classes of nitrogen compounds (see, for example, the chemistry of azides), they will not be taken up in this work.

Quinone imines have been investigated in great detail by Adams and coworkers. Their chemistry is closely related to that of quinones and of aromatic amines, and is discussed briefly in that connection in Chapter 3.

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